Tumor necrosis factor inhibitors: clinical utility in autoimmune diseases

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Tumor necrosis factor (TNF) production is amplified in several autoimmune disorders. In the 1990s, it became a validated therapeutic target used for the treatment of conditions such as rheumatoid arthritis and inflammatory bowel disease. Biologic drugs targeting TNF include engineered monoclonal antibodies and fusion proteins. Currently, there are 5 Food and Drug Administration–approved TNF inhibitors (infliximab, etanercept, adalimumab, certolizumab, and golimumab), representing close to $20 billion in sales. Clinical trials remain open to test their efficacy and safety compared with one another, as well as to measure clinical outcomes in different conditions and patient populations. The industry is also eager to develop biotherapeutics that are similar but cheaper than the currently existing biologics or are safer with higher efficacy; these are the so-called "biosimilars." Clinical utility of TNF inhibitors and indications of mono- or combined therapy with immunomodulators are reviewed here. Pharmacokinetics of the TNF inhibitors is affected by routes of administration, clearance mechanisms of immunoglobulins, and immunogenicity. Finally, strategies for management of treatment efficacy and increasing evidence for monitoring of serum concentration of TNF inhibitors are discussed, assessing for the presence of the antidrug antibodies and the different analytical methods available for laboratory testing. As clinical applications of the TNF inhibitors expand, and other classes join the revolution in the treatment of chronic inflammatory disorders, therapeutic drug monitoring of biologics will become increasingly important, with the potential to dramatically improve patient care and management. (Translational Research 2015;165:270–282)

Abbreviations: ACR = American College of Rheumatology; AS = ankylosing spondilytis; BIOBADASER = Spanish Registry for Adverse Events of Biological Therapies in Rheumatic Diseases; CD = Crohn's disease; CRP = C reactive protein; DMARDS = disease modifying anit-rheumatic drugs; FCRn = Brambell receptor; FcR = Fc receptor; HIV = human immunodeficiency virus; IBD = inflammatory bowel disease; Igs = Imunoglobulins; mAbs = monoclonal antibodies; NSAIDS = Non-steroidals anti-inflammatory drugs; PsA = psoriatic arthritis; PsO = plaque psoriasis; RA = rheumatoid arthritis; TNF = tumor necrosis factor; TB = tuberculosis; UC = ulcerative colitis

INTRODUCTION

History of therapeutic tumor necrosis factor inhibitors' development. During the last 2 decades, the chimerization and humanization of monoclonal antibodies (mAbs) have led to an exciting new class of biologic drugs. This class uses the central role that antibodies (aka immunoglobulins [Igs]) play in the adaptive immune system in recognizing and neutralizing antigens. As a class of drugs, the mAbs are engineered to recognize, inhibit, or remove human proteins involved in

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disease processes. Tumor necrosis factor α (TNF) is one such example. TNF is a cytokine with both proinflammatory and immunoregulatory functions. The role for TNF in rheumatoid arthritis (RA) was identified in 1991.[1] Soon after, clinical trials using a chimeric murine–human mAb directed against TNF showed significant clinical efficacy,[2,3] validating TNF as a therapeutic target. Since this time, the anti-TNF biologics have revolutionized the treatment of diseases such as RA, ankylosing spondylitis (AS), inflammatory bowel disease (IBD), and psoriasis.[4]

mAb structure and nomenclature. The basic structure of therapeutic mAbs, such as the TNF inhibitors, is based on the general structure of Igs. Ig molecules are constructed of 4 polypeptide chains including 2 identical heavy chains and 2 identical light chains. Functionally, each antibody can be divided into 2 domains: the variable region (Fab) and the constant region (Fc).[5] The Fab fragment contains the complementarity determining regions, which are specifically responsible for antigen binding. The Fc portion of the antibody determines the isotype of the Ig and is identified by the heavy chain (gamma, mu, alpha, delta, epsilon) and the light chain (kappa, lambda). The IgG isotypes in particular have effector functions attractive for therapeutics designed to clear harmful molecules, including complement activation and antibody-dependent cellular toxicity, which is mediated through interaction with specific Fc receptors (FcR). Clearance of IgGs occurs via proteolytic catabolism after receptor-mediated endocytosis in the reticuloendothelial system, resulting from interaction between the antibody and Fc gamma receptors I, II, or III. A second pathway functions to recycle IgGs, which requires binding to the Brambell receptor (FcRn). It is the balance between the proteolytic and FcRn pathways that determines IgG half-life.[4] To successfully design a therapeutic mAb, the Ig must be able recognize the human antigen (a function not typically desired in a normal immune response) and still be able to interact with the human FcRn.

Therapeutic mAbs have a standardized nomenclature based on their structure. Murine antibodies are named omab (eg, capromab). They were the first in clinical studies; however, their high immunogenic potential, low affinity for FcRn and short half-life compared with a human IgG were major drawbacks. Then, chimeric mAbs (minimum of 65% human) were developed, with murine variable regions and human Fc fractions; those are named ximab (eg, infliximab). Further improvements in therapeutic mAbs came with constructs containing murine hypervariable regions grafted into a human IgG structure, forming humanized mAbs (minimum of 95% human) with the designation zumab (eg, eculizumab). Lastly, fully engineered human antibodies have been developed, with the naming structure umab (eg, adalimumab and golimumab), that have similar properties to a human IgG and significantly reduced immunogenicity.

TNF inhibitors. There are currently 5[5] Food and Drug Administration (FDA)-approved TNF inhibitors available in the United States (Fig 1). Infliximab, the first biologic in its class, was approved in August 1998 for the treatment of severe Crohn's disease (CD). In 2002, it was also approved for treatment of refractory RA. Infliximab is a chimeric IgG1 mAb composed of a murine Fab region linked to a human IgG1 kappa constant region produced in cultured Chinese hamster ovary cells. Adalimumab is also produced in Chinese hamster ovary cells; however, it is composed of phage-display engineered human-derived variable regions. Golimumab, the newest TNF inhibitor to enter the market, is a human IgG1 kappa, produced in multiple glycoforms by a murine hybridoma cell line.[6,7] In contrast to the full-length mAbs, certolizumab is a humanized IgG4 Fab fragment produced by cell culture in *Escherichia coli* and then chemically linked to polyethylene glycol. This modification of the Fab fragment decreases metabolic clearance rates and extends the half-life of the molecule. Lastly, the most unique of the approved TNF inhibitors is etanercept. Etanercept is a recombinant fusion protein between the TNF p75 receptor and the Fc fraction of a human IgG1. It is currently the most prescribed TNF inhibitor in the US; however, it is not approved for IBD.

Since the early 1990s, numerous clinical trials have taken place to address the safety and efficacy of TNF inhibitors in multiple inflammatory conditions and to compare the use of one matched with the other. A total of 92 open clinical trials were identified by searching the term "TNF inhibitor" at http://www.clinicaltrials.gov as of May 13, 2014. The purpose of most of these trials is to evaluate the safety and efficacy of other biologics, such as rituximab (anti-CD20 mAb), vedolizumab (anti-$\alpha 4\beta 7$ integrin mAb), tofacitinib (small molecule inhibitor of JAK 3 kinase), and clazakizumab (anti-IL6 mAb), in patients who are refractory or intolerant to TNF inhibitors. These trials are also addressing outcomes in TNF inhibitor "switchers," or those patients who fail treatment with one biologic in the class and then move to another one. One new TNF inhibitor, named ozoralizumab, has recently completed phase II clinical trials in patients with RA; however, study results are not yet published. This humanized mAb fragment of approximately 38 KDa is a trivalent, bispecific single-domain antibody against TNF.[8]

Biosimilars. By 2015, several biologics will lose patent protection in Europe, including infliximab and