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Anti-TNF Therapy, from Rationale to Standard of Care: What Lessons Has It Taught Us?

Marc Feldmann and Ravinder N. Maini

In the mid-1980s, new molecular tools enabled the biology of cytokine expression and regulation to be studied. Our group uncovered a TNF-dependent cascade in active rheumatoid synovium, suggesting that TNF might be a therapeutic target; this concept was supported in an animal model of the disease. The proof of concept was a series of clinical trials, which have led to marked changes in the therapy of human rheumatoid arthritis and subsequently of other diseases. The work with TNF clearly demonstrated the importance of cytokines in medicine as well as the capacity of mAbs (or receptor fusion proteins) to be used long-term in large populations, thus changing the therapeutic landscape. *The Journal of Immunology*, 2010, 185: 791–794.

In the early 1980s, rheumatoid arthritis (RA), a disease affecting ~1% of the population worldwide, was a major clinical problem. Twenty-five years later, RA is far from curable, but it is much more manageable, less crippling, and less lethal. Research in immunology has had time to bear fruit and yield clinical benefit, resulting in reduced disease activity and progression.

RA is an autoimmune disease with chronic inflammation leading to joint destruction. The classical autoantibodies, or rheumatoid factors, have long been known; more recently discovered are IgG Abs to deaminated citrullinated proteins. The HLA association is well documented (1), with the shared epitope of HLA DR4/DR1 (2) suggesting the importance of the HLA association is well documented (1), with the shared epitope of HLA DR4/DR1 (2) suggesting the importance of The HLA association is well documented (1), with the shared epitope of HLA DR4/DR1 (2) suggesting the importance of the HLA association. The realization that cytokines augment HLA expression and Ag presentation to T cells in disease pathogenesis, as described by McDevitt and colleagues (3) and others.

The role of cytokines in disease was investigated following the realization that cytokines augment HLA expression and Ag presentation to T cells in local autoimmune disease sites, such as synovial joints. A hypothesis linking these processes was published in 1983 (4). Cytokine research was propelled by the successful biochemical purification and cloning of cytokine cDNAs. Molecular biology techniques also helped provide key therapeutics, such as engineered mAbs and receptor fusion proteins. The availability of specific Abs, many generously donated by the biotech industry, with Dr. Michael Shepard from Genentech (South San Francisco, CA) being a major donor, allowed us to identify which cytokines were present in rheumatoid disease tissue.

Our studies on cytokine mRNA expression in joints were contemporaneous with those of others, including J.M. Dayer, G.W. Duff, and G.S. Firestein (5–9). The results were more complex than anticipated, as essentially all cytokines assessed were present, including many proinflammatory cytokines. Thus, merely studying cytokine expression in joints was not sufficient to define the elusive therapeutic target. However, by using a tissue culture system to analyze the complex regulation of cytokines in the rheumatoid synovium, TNF-α was identified as a therapeutic target. First, culturing synovial tissue cells revealed abnormally prolonged cytokine production, a finding in keeping with a chronic disease. Second, the use of neutralizing anti-TNF Abs demonstrated the existence of a TNF-dependent proinflammatory cytokine cascade. These experiments, performed in the late 1980s by Research Fellows in our laboratory, Glenn Buchan and Fionula Brennan, have been fully described in review articles (10, 11). Important confirmation of the importance of TNF came from the collagen-induced arthritis model. Although widely accepted now as the best (in reality, least bad) mouse model of RA, it has limitations in predicting the success of clinical trials. Nevertheless, using hamster anti-mouse anti-TNF mAb generously donated by Robert Schreiber (Washington University, St. Louis, MO), Richard Williams and colleagues (12) showed that disease activity was ameliorated when anti-TNF Ab was administered post disease onset.

We believe that having two research leaders with similar interests and overlapping expertise and many talented Research Fellows, support staff, and well-equipped laboratories with long-term funding, was very important in the efficient progress of this research project toward the clinic. We were not aware at the time that our efforts would lead to the first effective use of molecular biological techniques to define an inflammatory therapeutic target and the first use of modern biological therapeutics (mAbs and receptor fusion proteins) for long-term treatment of a large number of patients.

Having defined TNF as a therapeutic target in preclinical experiments, we were very keen to test our novel, but for many a heretical, idea that a single cytokine could drive a multicytokine, multicellular chronic disease. Arising from the work of Anthony Cerami, Bruce Beutler, and Kevin Tracey (13, 14), many companies had produced anti-TNF inhibitors, both mAbs and TNFR fusion proteins, for the treatment of sepsis, but without success when applied in clinical trials. We were...
Fortunately able to interest an ex-colleague, James N. Woody, Chief Scientist at Centocor (Malvern, PA), a company specializing in mAbs, to work with us in RA clinical trials. John Ghrayeb at Centocor had chimerized (made three-fourths human by using molecular biology techniques to graft human Fc and part of Fab onto a mouse Ab) a mouse anti-TNF monoclonal generated by Jan Vilcek (15). This therapeutic, cA2, was later known as infliximab (Remicade, Centocor).

Our first clinical trial of infliximab in RA was in April 1992, at Charing Cross Hospital (London, U.K.). This was an open-label trial due to concerns about safety of a blinded clinical trial. Infliximab was well tolerated with no short-term safety signals and impressive efficacy, but as the Ab metabolized, all patients relapsed by 12–18 wk. In further extension studies, we were able to treat some patients for several more courses and demonstrate clinical benefit lasting over a year (16, 17). Next, we performed a formal double-blind placebo-controlled randomized trial with three European collaborators, Ferdinand Breedveld, Joachim Kalden, and Josef Smolen, in 1993. A single infusion, with either a previously used effective dose (10 mg/kg) or a tenth of that, was used; both were accompanied by dramatic dose-related efficacy over 4 wk compared with placebo (18). From this trial, we were able to perform a series of studies on the mechanism of action of the anti-TNF Ab.

By the time the extensive, longer trials designed for drug registration were being planned (1994), the work of Michael Weinblatt and others had led to low-dose methotrexate (MTX) being widely used for the treatment of RA as the gold standard (19). But most patients could not remain on MTX long-term, and an emerging unmet need was treatment of MTX-resistant patients. Thus long-term randomized controlled and registration trials were performed in patients with persistent inflammatory activity and an incomplete response to ongoing treatment with low-dose MTX. Initially, a 3-mo treatment with a 3-mo follow-up protocol compared MTX plus anti-TNF, with anti-TNF at three doses or MTX alone. The MTX plus anti-TNF was far superior and at low anti-TNF doses (1 mg/kg) was clearly synergistic, with augmented benefit clear at 3 mg/kg and discernable at 10 mg/kg (20). Thereafter, phase III registration trials were performed in combination with MTX, and consequently, the label (permitted use) of infliximab in RA is with MTX (21).

One of the key clinical findings was that the combination treatment, MTX plus anti-TNF, but not MTX alone, protects joints from progressive damage to cartilage and bone destruction, as evaluated by serial radiographs. This occurred at all concentrations of anti-TNF/MTX tested. Efficacy correlated with blood concentration of the Ab. Subsequent secondary loss of efficacy at the 1 mg/kg dose administered as monotherapy clearly reflected the induction of an anti-chimeric Ab response, with MTX reducing immunogenicity in the cotherapy arm (20). It was striking that results with the TNFR fusion protein etanercept (Enbrel, Amgen, Chesterbrook, PA and Wyeth, Madison, NJ) (22) and the fully human monoclonal adalimumab (Humira, Abbott, Abbott Park, IL) also demonstrated marked joint protection and the marked effect of added MTX (23) in the absence of Abs to the therapeutic agent.

With the very marked differences between treated and control groups and the high specificity of the treatment, it was possible to perform a detailed analysis of biomarkers and mechanism of action following TNF blockade. Our own studies, and those of other investigators, are continuing to illuminate the role of TNF in immune-mediated diseases (18, 24–26). Of particular note are the following studies:

1) Within hours of anti-TNF administration, the elevated levels of IL-6 in serum plummet virtually to baseline, thus confirming the existence of a TNF-dependent cytokine network in RA patients in vivo, a hypothesis supported by other studies (24).
2) Retention of 111In-radiolabeled neutrophils in joints is reduced, as is expression of adhesion molecules and chemokines, supporting a role for TNF in cell recruitment (27).
3) The production of vascular endothelial growth factor, a cytokine implicated in angiogenesis, is reduced and partly dependent on TNF (28).
4) Rapid normalization of low hemoglobin, high platelet counts, and fibrinogen concentration and restoration of abnormal regulatory T cell function demonstrate a role for TNF in the loss of homeostasis of the immune and hemopoietic systems observed in disease (29).
5) Destructive enzymes (e.g., matrix metalloproteinase 3) are reduced, and osteoprotegerin levels are restored, pointing to the TNF dependence of pathways of matrix destruction in cartilage and bone (30, 31).
6) Although there is a falloff of response to anti-TNF with time, some patients have remained responsive to anti-TNF for over 5 y (32). This indicates that cytokine networks in RA evolve slowly, if at all, and if TNF is blocked, its pivotal role in orchestrating the inflammatory response is not displaced by another proinflammatory cytokine.

Demonstrating that a new therapeutic in clinical trials is effective completes the translation of science into medicine. But there remains a need for the knowledge to be disseminated and, most importantly, for the new therapeutic to be used effectively and with minimal harm. These are significant hurdles. First, not all clinical trials provide the data clinicians want and need for application in practice. Secondly, new therapeutics can be prohibitively priced. Our clinical trials in MTX poor responders did provide much of the information clinicians needed, but not all. The cost of anti-TNF therapeutics has restricted their use, but the degree of clinical benefit, including joint protection and the lack of alternatives at the time (1998/1999 onwards) has meant that it has become the standard of care for moderate to severe RA. Cost-benefit analyses, such as provided by the United Kingdom’s National Institute for Clinical Excellence, have documented the benefit of these therapeutics, even at their high cost ($15,000–20,000/y) (33). By now, ~2 million patients have been treated with the various anti-TNF therapeutics.

It is of significant interest that in clinical trials of all five anti-TNF biologics that have been licensed by the U.S. Food and Drug Administration, only a proportion of patients respond to treatment. The percentage of primary nonresponders varies but is ~30%. Why some patients never respond is intriguing, and efforts have been made using biomarker studies to identify response to therapy, but none have been validated. A study based on a genome-wide association scan suggests a complex multigenetic basis for response or resistance to therapy (34–36). Secondary nonresponsiveness after a successful initial response does appear, in part, to be related to the immunogenicity of the therapeutic Ab (37).

The obvious impact of the discovery of anti-TNF therapy is on RA patients and their care. But the success of anti-TNF...
in RA prompted its use in other related diseases, for which it has also been successful. Anti-TNF therapy is now an approved treatment for immune-inflammatory diseases, such as juvenile RA, ankylosing spondylitis, psoriatic arthritis, Crohn’s disease, ulcerative colitis, and psoriasis. In all of these, the effect on patients has been dramatic (e.g., the healing of fistulas in Crohn’s disease) and has greatly improved quality of life (38, 39).

The successful long-term use of anti-TNF in a chronic disease has challenged a prejudice of the pharmaceutical industry that patients do not tolerate repeated injections and prefer orally available drugs. The good efficacy/safety ratio of biologicals (mAbs and receptor fusion proteins), patient compliance, and high profitability in the market, not only of anti-TNF, but subsequently anti-CD20, anti-vascular endothelial growth factor, and anti-HER2, have highlighted the increasing importance of biological therapeutics. The invention of anti-TNF therapy has contributed to this change in the therapeutic landscape and the practice of medicine well beyond its impact on patients directly treated.

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Disclosures

M.F. and R.N.M. are named on patents for anti-TNF therapy. M.F. owns shares of Johnson & Johnson, Inc., and Centocor (a subsidiary of Johnson & Johnson, Inc.) is a manufacturer of anti-TNF Abs.

References


