Cytokine Blockade as a New Strategy to Treat Rheumatoid Arthritis

Inhibition of Tumor Necrosis Factor

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Rheumatoid arthritis (RA) is a common, frequently severe, chronic inflammatory disease. Although the cause of RA remains unknown, recent advances in understanding its pathogenesis have been substantial. Despite the use of a variety of medications, particularly methotrexate, treatment of RA is not fully effective in most patients. Until recently, insights into inflammatory mechanisms in RA had not been successfully translated into novel classes of therapeutic agents. This gap now will likely be bridged in the form of a new strategy for treating RA-cytokine blockade. Although a variety of cytokines are important in the pathogenesis of RA, tumor necrosis factor (TNF) seems to play a pivotal role. Neutralizing TNF in patients with RA, by means of soluble TNF receptors or anti-TNF monoclonal antibodies, has proven to be a powerful means of controlling disease activity. Studies are in progress to obtain additional information regarding long-term safety of TNF blockade and its effects on disease progression.

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Rheumatoid arthritis (RA) affects 0.5% to 1.0% of the population and causes not only enormous morbidity but also substantial mortality. Most people with chronic RA experience work disability, and the total costs per year of this disease have been estimated at almost $9 billion in 1994 dollars (reviewed by Callahan). Despite intensive study, the cause of RA remains unknown, and RA is defined using a set of empirically derived clinical criteria. In general, the treatment of RA has not been logically grounded on a sound understanding of pathogenesis. Instead, a heterogeneous array of anti-inflammatory and immunosuppressive agents has been used, many borrowed from other fields of medicine. Putative explanations for their effects on the biological mechanisms of RA have often followed, rather than preceded, demonstration of clinical efficacy. Despite such limitations, substantial strides have been made in the medical management of RA, including extensive use of methotrexate, aggressive treatment of RA earlier in its course, and development of effective treatment combinations with methotrexate and other traditional medications. Nevertheless, treatment of RA remains insufficiently effective and distressingly toxic for many patients. New strategies are clearly required.

RECENT CHANGES IN UNDERSTANDING RA: A FRAMEWORK FOR RETHINKING APPROACHES TO ITS MANAGEMENT

Although RA has typically been viewed as an autoimmune disease, this concept of its pathogenesis is still not supported by convincing demonstration of a unique autoantigen. Humoral and cellular immune responses to autoantigens, such as production of rheumatoid factors, occur in RA. However, none of the autoreactive phenomena observed in RA are specific to RA, present in all patients, or clearly linked to the destruction of cartilage and bone, the all-too-frequent consequence of long-term rheumatoid synovitis. The role of T cells in RA is currently a matter of considerable debate (reviewed by Fox). Although T cells are abundant in the inflamed joint, critically involved in animal models of RA, and implicated in human RA by the association of class II major histocompatibility complex (MHC) alleles with RA, a T-cell–centered view of the disease has not yet led to clearer insight into...
the etiology of RA or breakthroughs in its treatment. Although the RA-MHC association seemed to suggest that T-cell recognition of an arthritogenic microbial antigen or autoantigen was an essential component of the pathogenesis of RA, this hypothesis remains unproved, and other explanations for the role of MHC in RA are receiving attention. T-cell–derived lymphokines are not the most abundant cytokines in synovial tissue or fluid, and attempts to treat RA using novel T-cell–depleting biological therapeutics, such as monoclonal antibodies, have been surprisingly ineffective.

Such disappointments do not exclude a role for T cells in this disease but might instead point to our incomplete appreciation of the complex nature of the synovial T-cell response in RA. Nevertheless, a balanced view of the pathogenesis of RA, and of appropriate molecular targets for novel therapeutic strategies, must also focus on the roles of other important cellular components of RA synovium and on their secreted mediators. An alternative model for understanding RA, distinct from traditional definitions of autoimmunity, is as a chronic tissue-specific inflammatory process to which a variety of immune responses can contribute. In such a model, unique elements of RA arise from the interactions between the variety of leukocytes that invade the joint and the native cellular components of joint tissue (Figure 1 and Table 1).

The synovium contains 2 principal cell populations, termed type A and type B synoviocytes. Type A synoviocytes belong to the monocyte-macrophage family, with potent phagocytic ability and the capacity to secrete large quantities of proinflammatory cytokines. Type B synoviocytes are specialized fibroblasts that produce hyaluronic acid and collagen. In an inflammatory milieu, type B synoviocytes can also secrete cytokines, proteases, and other inflammatory mediators. Type A and B synoviocytes are present in greatly increased numbers in RA synovium, along with other functionally important cell populations (Table 1). In addition, neutrophils in synovial fluid and chondrocytes in adjacent articular cartilage are important contributors to inflammatory pathways in the RA joint.

**Cytokines in RA: Critical Mediators of Acute and Chronic Inflammation**

Cytokines are proteins that function as intercellular messengers in inflammation, immune responses, and tissue repair or remodeling. During the past 2 decades, dozens of cytokines and their receptors have been discovered, cloned, and studied in human disease. Many have been classified as interleukins (ILs), whereas others carry designations associated with one of their biological activities, such as tumor necrosis factor (TNF), also termed TNF-α. Although cytokines are a dauntingly heterogeneous and complex group of molecules, some general principles regarding their biological features are worth summarizing:

1. Production of cytokines is generally not constitutive but is inducible as an activation response of cells to specific stimuli, such as microbial products or other cytokines.

2. Although individual cytokines might be characteristically produced by specific cell types, such as TNF by monocyte-macrophage lineage cells, most cytokines can be
sythesized by a heterogeneity of cell types.

3. Cytokines produce biological and pathologic effects by binding to specific cell surface receptors that contain 1 or more protein subunits and are linked to signal transduction systems that ultimately regulate transcription of specific, inducible genes.

4. Cytokines are pleiotropic (functionally heterogeneous) in their effects, depending on the cellular target on which they act and which concurrent activating or inhibitory factors, including other cytokines, are present. Existence of more than 1 receptor type for an individual cytokine explains only a small component of this pleiotropy.

5. Cytokines possess extensive redundancy, or overlap, of their effects.

6. Cytokines act locally, in the tissue where they are synthesized, most of the time, unlike many conventional hormones. However, when produced in abundance, some cytokines, especially those with critical roles in inflammation and host defense such as IL-1 and TNF, have important and wide-ranging systemic effects.

7. Although generally functional as secreted molecules, some cytokines can also be biologically active in a membrane-bound form.

8. Physiological regulation of cytokine production and function is controlled at many levels, including secretion of cytokine receptor antagonists and production of soluble cytokine receptors. Examples include the IL-1 receptor antagonist and the soluble TNF receptor (sTNF-R).

In RA, cytokines are involved in almost all aspects of synovial inflammation and destruction of articular tissues. Table 2 lists some of the many cytokines detected in RA synovial tissue or fluid. T-cell-derived cytokines are present at lower concentrations than are some of the monocyte-derived cytokines. This does not exclude an important role for such T-cell factors, which might exert potent local effects even when produced intermittently and in small quantities. Nevertheless, it is clear that TNF and IL-1 are 2 of the dominant cytokines in RA.

The total number of distinct cytokines in the RA joint is actually severalfold greater than that listed in Table 2. For example, IL-8 is only one of a large family of chemotactant cytokines or chemokines that attract leukocytes of various types through activated and hyperplastic synovial endothelium into synovial tissue and fluid. Interleukin 10 and transforming growth factor β are examples of cytokines that could have anti-inflammatory potential in RA and other diseases. Others in this category include IL-4 and IL-13, of which the former is found in RA synovium. An important point in this regard is that the presence of a cytokine in a lesion does not prove that it contributed to inflammation or tissue damage present in that lesion. Some cytokines might in fact be retarding these processes, albeit with limited success in RA.

Table 2. Cytokines Detected in Rheumatoid Arthritis Synovial Tissue or Fluid

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Source</th>
<th>Target</th>
<th>Abundance</th>
<th>Effect on Inflammation or Tissue Damage</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNF</td>
<td>M</td>
<td>Multiple</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>IL-1β</td>
<td>M</td>
<td>Multiple</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>IL-6</td>
<td>M, F</td>
<td>Multiple</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>IL-8</td>
<td>Multiple</td>
<td>Neutrophils</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>IL-10</td>
<td>M, T</td>
<td>T</td>
<td>++</td>
<td>–</td>
</tr>
<tr>
<td>IL-12</td>
<td>M</td>
<td>T</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>IL-15</td>
<td>F, M</td>
<td>T</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>IL-2</td>
<td>T</td>
<td>T</td>
<td>+/−</td>
<td>+</td>
</tr>
<tr>
<td>IL-17</td>
<td>T</td>
<td>F</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>IFN-γ</td>
<td>T</td>
<td>Multiple</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>TGF-β</td>
<td>Multiple</td>
<td>T</td>
<td>++</td>
<td>−</td>
</tr>
<tr>
<td>GM-CSF</td>
<td>M, T</td>
<td>Multiple</td>
<td>++</td>
<td>++</td>
</tr>
</tbody>
</table>

*TNF indicates tumor necrosis factor; IL, interleukin; IFN, interferon; TGF, transforming growth factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; M, monocyte/macrophage; F, fibroblast; T, T lymphocyte; −, inhibitory effect; +, low abundance/mild effect; ++, moderate abundance/moderate effect; and ++++, high abundance/high effect.

Subsequent sections of this review focus on the role of TNF in RA. However, it is worth bearing in mind that IL-1 and TNF have overlapping and synergistic roles in RA. Nevertheless, some of the effects of these 2 cytokines and the mechanisms by which they are regulated are distinct. Therefore, interruption of IL-1 or TNF activity potentially represents 2 different novel approaches to the treatment of RA.

**BIOLOGICAL FEATURES OF TNF**

Tumor necrosis factor is a fascinating cytokine that illustrates each of the 8 points about the biological features of cytokines listed in the previous section. Originally discovered as a factor induced by microbial lipopolysaccharide that can induce regression and cell death of some tumors, and shortly thereafter characterized as a mediator of cachexia induced by chronic infection or tumors, it is now known to mediate a vast spectrum of biologic effects. Tumor necrosis factor is a member of a large and growing family of secreted and cell membrane–bound proteins, including the closely related cytokines lymphotoxin α and β. Although macrophages are a primary source of TNF, a variety of cell types can synthesize this molecule, including lymphocytes, neutrophils, keratinocytes, mast cells, and some tumors. Tumor necrosis factor is translated as a membrane-associated 233–amino acid prohormone, following which a 76–amino acid signal peptide is proteolytically cleaved off to yield the mature 17-kd TNF molecule. The larger forms can also be found as a transmembrane protein in some cell types. The genes for TNF and lymphotoxin α (formerly termed TNF-β) are closely linked to the MHC genes.

In animals and humans, TNF induces a plethora of inflammatory and catabolic effects, including fever, shock, tissue injury, energy substrate mobilization, cachexia, anemia, and induction of hepatic acute-phase proteins. The biologic effects of TNF are caused by direct
actions on multiple target tissues and induction of other cytokines, such as IL-1, IL-6, and IL-8. Tumor necrosis factor–induced recruitment of leukocytes to localized inflammatory lesions is produced by multiple actions, including induction of adhesion molecules, chemokines, and even angiogenesis. Tumor necrosis factor can potentiate lymphocyte activation, and it is produced by activated lymphocytes. All these properties likely explain the importance of TNF in host defense against a variety of pathogens, especially intracellular bacteria and parasites, and possibly also some viruses (reviewed by Vassalli).

ROLE OF TNF IN RA

Tumor necrosis factor is present at biologically significant levels in RA synovial tissue and fluid but not in osteoarthritic synovium or systemic lupus erythematosus kidney tissue. Furthermore, the level of TNF in synovium seems to parallel the extent of both inflammation and bone erosion. As shown schematically in Figure 1, TNF triggers several of the most central and critical events in the acute and chronic synovial inflammation and ultimate tissue destruction characteristic of RA, including induction of multiple additional cytokines and chemokines, expression of adhesion molecules and increased levels of class I MHC determinants, synthesis and release of proteases and prostaglandin E2 by synovial fibroblasts (which is important in erosion of cartilage and bone), and synovial neangiogenesis. (Interleukin 1 shares some of these properties of TNF, including stimulation of the secretion of proteases, inflammatory cytokines, and prostaglandin E2. Some data suggest that monocytes from patients with early RA hyperproduce TNF when activated. Taking all the data into consideration, one can reasonably conclude that TNF is one of the most important cytokines in the pathogenesis of RA.

TNF RECEPTORS

Shortly after discovery of TNF, several laboratories established that this cytokine interacts with target cells by means of high-affinity, saturable receptors, which also bind lymphotoxin α. Results of experiments using monoclonal antibodies suggested the existence of 2 distinct forms of the TNF receptor, which became known as p55 (or p60) and p75 (or p80). Tumor necrosis factor receptors are part of a family of cell-surface proteins that contain a cysteine-rich extracellular domain and a more variable cytoplasmic domain with complex signal-transduction properties (reviewed by Bazzoni and Beutler). Biological responses mediated by the 2 types of TNF receptors on RA synovial fibroblasts overlap substantially, and this is likely to be true of other cell types that are targets of TNF. In RA but not osteoarthritis synovium, both the p55 and p75 receptors are strongly expressed. Most type A (macrophage-derived) and type B (fibroblastic) synoviocytes in the lining layers of RA synovium express p55 (more so than p75), and many of these cells also produce TNF. In RA synovial lymphoid aggregates and at the cartilage-pannus junction, p55 and p75 are abundant. Thus, all elements for local production and local utilization of TNF are present in the lesions of RA. Tumor necrosis factor receptors are also produced naturally as soluble molecules, probably by proteolytic cleavage of the p55 and p75 extracellular domains at the cell membrane. Such soluble receptors inhibit TNF action by competing with cell surface receptors for binding of TNF, thereby blocking the biologic effects of TNF. Patients with RA have circulating levels of sTNF-R that are higher (generally 2-6 ng/mL for each type of sTNF-R) than those in sera of healthy individuals, patients with osteoarthritis, or even patients with other forms of inflammatory arthritis. sTNF-R levels are severalfold higher than are those in serum, with levels in RA again higher than those in other forms of arthritis. In vitro and probably in vivo sTNF-R can regulate effects of TNF relevant to the pathogenesis of RA, but this is not sufficient to neutralize the high levels of bioactive TNF in patients with RA. Nevertheless, the available data provide a sound conceptual basis for strategies to treat RA by pharmacological elevation of sTNF-R levels.

THERAPEUTIC INHIBITION OF TNF IN ANIMAL MODELS AND HUMAN DISEASE

In animal models of septic shock, either anti-TNF monoclonal antibody or sTNF-R is effective in reducing mortality, but the need for administration before exposure to bacterial products likely accounts for difficulty in demonstrating clinical benefit in human trials. Either approach to TNF neutralization is effective in murine collagen–induced arthritis not only in preventing disease but also in reducing ongoing joint inflammation. Moreover, anti-TNF antibody was demonstrated in 1989 to inhibit production of IL-1 by synovial cells in culture. The reciprocal regulation of TNF production by IL-1 was not observed in this system, although IL-1 seems to induce TNF during the development of fever.

Some conventional and experimental pharmacological treatments for RA (that are not direct TNF antagonists) might work in part through some degree of reduction in TNF levels, although this was not known at the time that their clinical effects were discovered. For example, cyclooxygenase inhibitors can attenuate many of the acute effects of TNF. Corticosteroids, among their many anti-inflammatory actions, partially suppress production of several cytokines, including TNF (reviewed by Barrera et al). Antimalarials, gold compounds, and sulfasalazine can suppress TNF production by monocytes in vitro, but D-penicillamine, methotrexate, and azathioprine do not seem to affect TNF production or function. Patients with RA treated with methotrexate or azathioprine showed no change in serum TNF levels during responses to treatment in 24 weeks, although IL-6 levels declined. Production of TNF was reported to be inhibited by several agents not yet fully evaluated for treatment of RA, including thalido-
mide, pentoxifylline, and tacrolimus (FK 506). The anti-inflammatory cytokine IL-10, which is under investigation as a possible treatment for RA, decreases TNF production by RA synoviocytes, and IL-4 has similar effects. However, IL-10, in contrast to IL-4, augments expression of the p75 TNF receptor on normal monocytes and on RA synovial fluid macrophages, with consequent increases in TNF-induced production of IL-1β by these cells. This result raises questions about the potential value of treating RA with IL-10. More data are needed regarding the effects of these and other agents on TNF production and function. Such information might be useful in developing combination treatments for RA that would include a TNF blocking agent and other drugs with different anti-inflammatory mechanisms.

TREATMENT OF RA WITH MONOCLONAL ANTI-TNF ANTIBODIES

The information described in the preceding sections has set the stage for studies to determine whether human RA can be treated by direct neutralization or blockade of TNF. Monoclonal antibodies to TNF were the first such approach to be evaluated clinically. The best-studied antibody is cA2 (infliximab), a chimeric mouse-human immunoglobulin (IgG1) molecule. Another humanized anti-TNF antibody tested in RA is CDP571 (reviewed by Kavanaugh). The studies using cA2 have shown impressive and rapid clinical effects in established RA, in open trials and in double-blind, randomized, placebo-controlled trials. cA2 is administered as an intravenous infusion, and doses of 1 to 20 mg/kg have been studied for up to 14 weeks. The response is dose-dependent, with a single dose of 10 to 20 mg/kg able to generate clinically significant responses that persist for at least 1 month (median duration, 8 weeks) in 80% of patients. A striking degree of improvement is generally seen, with greater than 50% change in all clinical variables and in C-reactive protein and erythrocyte sedimentation rate. Retreatment is effective, although the duration of responses seems to decrease, possibly because of development of antibodies to the anti-TNF monoclonal antibody. cA2 is effective when added to methotrexate in patients with RA who are refractory to methotrexate, and methotrexate use might prolong the duration of responses to cA2, possibly retarding the human antichimeric antibody response. Although TNF neutralization, it seems that the most frequent difficulty caused by human antichimeric antibody is likely to be diminished efficacy of cA2. Occasionally patients have developed infections (in rare cases, serious ones) during treatment, but it is not yet clear whether the incidence of infection will be greater than in other groups of patients with RA. Some patients with RA treated with cA2 have developed malignancies, including at least 3 cases of hematologic neoplasms, which probably occur at an increased frequency in RA. cA2 might accelerate clinical presentation of neoplasia by interfering with antitumor host-defense mechanisms. Of particular interest has been the appearance of antinuclear antibodies in a subset of patients and the less frequent occurrence of a transient systemic lupus erythematosus–like syndrome. The (NZBxNZW)F1 mouse, which develops murine lupus, tends to produce low levels of TNF, possibly on a genetic basis, and administration of TNF to such animals induces a significant delay in the development of glomerulonephritis. In contrast, transgenic mice that constitutively overexpress TNF develop inflammatory arthritis but no systemic lupus erythematosus–like lesions. These fascinating findings in animals and humans suggest that the ambient level of TNF might have a hitherto underappreciated capacity to control the form in which autoimmunity is expressed as a specific syndrome or disease.

The mechanisms of anti-TNF effects (and toxic effects) in RA need to be further explored. Findings to date (reviewed by Camussi and Lupia) include decreases in serum acute-phase reactants, IL-1, IL-6, and soluble leukocyte-endothelial adhesion molecules. In synovium, lymphocyte infiltration and adhesion molecule expression are reduced. In addition to the multiple potential anti-inflammatory effects of TNF neutralization, it seems that cA2 could mediate complement-dependent lysis of cells that bear membrane-bound TNF. Whether cA2 can retard erosion of cartilage...
and bone in human RA by reducing secretion of tissue-destructive mediators is not yet established, although preliminary findings have been encouraging.

**TREATMENT OF RA WITH sTNF-R**

A second approach to TNF blockade in RA has been administration of a modified, genetically engineered form of the p75 TNF receptor, termed etanercept (reviewed by Moreland). Etanercept is a dimeric molecule that contains two p75 sTNF-R extracellular domains attached to the Fc portion of human IgG1 (Figure 2). This dimeric molecule has greater TNF-binding affinity and a longer half-life (90 hours) than does the sTNF-R monomer. In a preliminary dose-finding study, etanercept was given to patients with RA at an initial intravenous dose of 4 to 32 mg/m², followed by biweekly maintenance doses of 2 to 16 mg/m² administered subcutaneously. A small placebo group allowed for sufficient comparison of clinical and laboratory variables to suggest efficacy of etanercept, especially at higher doses. Subsequently, 2 multicenter, placebo-controlled trials have demonstrated clinical benefit of this agent in refractory RA. In the first study, etanercept or placebo was administered to patients who previously had not responded to conventional disease-modifying agents and who received only nonsteroidal anti-inflammatory drugs, analgesics, and low-dose corticosteroids concurrently. At 16 mg/m² (but not at ≤2 mg/m²) given subcutaneously twice weekly, substantial improvement was seen in multiple clinical and laboratory variables in 75% of treated patients compared with 14% of patients who received placebo. Etanercept was administered for 3 months, and after drug discontinuation the improvements observed were not maintained during subsequent 2-month follow-up. A subsequent study indicated that therapeutic benefit was maintained during a 6-month treatment interval. Ongoing studies are evaluating etanercept in early RA and when added to methotrexate in refractory RA. In patients with persistently active RA despite methotrexate treatment, the combination of methotrexate and etanercept treatment is safe and effective for at least 24 weeks. A p55 sTNF-R has also been tested in patients with RA, but only limited data suggesting efficacy and safety are available. Unlike the p75 sTNF-R, the p55 sTNF-R (lenercept) is immunogenic, although molecular modifications of its conformation might mitigate this problem.

Etanercept binds TNF, rendering it biologically inactive but still present in tissue fluids. In fact, the half-life of the TNF complexes is longer than that of free TNF. More information is required concerning the details of how etanercept treatment alters the pathophysiological mechanisms of RA and whether the therapeutic mechanisms differ from anti-TNF treatment. Studies using a p55 sTNF-R show that the concentration of this agent required to block release of collagenase and prostaglandin E₂ by synovial fibroblasts is 100-fold lower than the concentration required to inhibit T-cell activation. This reflects response of T cells to membrane-bound TNF, which is more difficult to block with a soluble receptor. One intriguing difference between sTNF-R and anti-TNF monoclonal antibodies is the ability of sTNF-R to also bind, and undoubtedly neutralize, lymphotoxin α, which uses the same receptors as TNF.

To date, etanercept has been associated with only mild toxic effects, including injection-site reactions and mild upper respiratory tract symptoms, but no formation of neutralizing antibodies to TNF receptor. There have been a few cases of nonneutralizing antietanercept antibodies, which had no apparent clinical effect. With further experience, etanercept use might be found to induce immunologic changes such as anti-DNA antibodies, as has occurred with cA2 use.

**FUTURE DIRECTIONS**

Tumor necrosis factor blockade will likely become a major therapeutic advance in the treatment of RA and will probably be widely used in this disease. Extension of this approach to other conditions will require careful evaluation in each specific disease because animal models have proven that inhibition of TNF action can, in some instances, accelerate autoimmunity. Nevertheless, TNF blockade will probably be an important approach in the treatment of Crohn disease and, undoubtedly, for several other autoimmune or inflammatory diseases. In RA, issues of long-term efficacy, safety, and mechanisms of action of each approach to TNF blockade need to be addressed. Possibilities for synergistic efficacy with use of methotrexate, IL-1 blockade, or even antilymphotoxin monoclonal antibodies must be investigated further. Additional pharmacological approaches to block TNF function are worth exploring given the generally high cost of biological agents.

The potential for a more problematic profile of toxic effects with long-term treatment needs to be considered. Problems with opportunistic infections, especially those caused by intracellular pathogens such as mycobacteria and Listeria, can be expected in view of the role of TNF in host defenses against such organisms. Given the combined role of TNF and lymphotoxin α in the development of peripheral lymphoid tissues, maintenance of the organizational integrity and host defense function of these tissues might be compromised by prolonged TNF blockade. Because TNF blockade does not cure RA but requires ongoing treatment to maintain efficacy, late-occurring toxic effects will pose new therapeutic challenges. Surprises and new insights, along with better control of chronic joint inflammation, await both the scientist and the clinician as potent blockade of one of nature’s most powerful cytokines moves into clinical practice.

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