Introduction: New Treatment Paradigms in Rheumatoid Arthritis

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Rheumatoid arthritis (RA) is a systemic autoimmune disease predominantly of the joints, although many other organs can also be affected. Rheumatoid arthritis is common: more than 2 million US adults have it.[1] RA usually symmetrically affects the small joints of the hands and feet, although the wrists, elbows, shoulders, knees, hips, and cervical spine are frequently involved as well. Chronic and/or intermittent inflammatory arthritis may progressively destroy the affected joints, leading to significant disability and impaired quality of life.[2] While the historical approach to treatment entailing a slow progression from reliance on nonsteroidal anti-inflammatory agents (NSAIDs) to more aggressive medications was perhaps effective for some patients, in many others, the results were far from optimal. The introduction of anti-tumor necrosis factor alpha (anti-TNF-α) agents for the treatment of RA has ushered in a new era of targeted biologic treatments in rheumatology, while also serving to catalyze the shift to aggressive treatment protocols involving earlier treatment and the use of multiple medications in combination. Although the longer-term effects of new treatment approaches are not yet known, early results appear very favorable.

The pathogenesis of RA is complex, and despite important strides in immunology, it is insufficiently understood. Clearly, many different cell types and soluble mediators are participating in the inflammatory process and contributing to the irreversible bony destruction that is evident.[3-6] Furthermore, disease pathogenesis is likely to vary at different stages (triggering, amplification, chronic inflammation, and relapses). Although a comprehensive review of the pathogenesis of RA is not within the scope of this supplement, intensive research has focused on several immunologic processes that represent attractive targets for therapeutic intervention. Specifically, interactions between antigen-presenting cells (APCs, including B cells) and T cells, and the secretion of potent proinflammatory cytokines, are central in joint inflammation and destruction. While treatment with biologic response modifiers (BRMs) targeting these pathways are not curative, the actual effective translation of basic research efforts into patient care has been exciting and dramatic. Furthermore, the clinical effectiveness of these novel BRMs and their successful use in a large number of patients suffering from RA, psoriatic arthritis, or ankylosing spondylitis have stimulated continued investment in research efforts in the field. These will no doubt lead to additional treatments for RA, and probably for other challenging rheumatic diseases as well.

In this Rheumatoid Arthritis Consult Collection, several prominent clinician-researchers have joined to provide an overview of state-of-the-art approaches for the treatment of RA. Dr. Arthur Kavanaugh reviews current strategies, with a focus on classical NSAIDs and traditional, oral disease-modifying antirheumatic drugs (methotrexate). NSAIDs and glucocorticoids still play important roles in the treatment of RA, in treating disease exacerbations, and as a bridge until slower-acting, disease-modifying agents take effect. Dr. Kavanaugh reminds us that despite the hope that cyclooxygenase-2 (COX-2)–selective NSAIDs would control inflammation with fewer gastrointestinal side effects, evidence indicating promotion of cardiovascular disease by COX-2–selective NSAIDs encouraged the voluntary withdrawal of 2 medications from this class. There is an important message in the COX-2 story, reminding physicians of unexpected side effects that can appear during clinical trials of new medications, or subsequently, when the drug is in widespread use.

Dr. Joseph Markenson's article centers on the safety and efficacy of BRMs, including TNF-α inhibitors, interleukin-1 (IL-1) inhibitors, and B-cell depletion therapy. While Dr. Markenson points out that there are still concerns about long-term efficacy and safety, he emphasizes that over the past few years these medications have demonstrated significant clinical efficacy in research settings and in actual clinical use.

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Cytokines are pivotal mediators in the joint inflammation present in RA patients[7]; of those, TNF-α and IL-1 are believed to play a central role. Several anti–TNF-α inhibitors, including adalimumab, etanercept, and infliximab, are approved for the treatment of RA, differing in their mode of administration (subcutaneous versus intravenous), mechanism of inhibition (antibody versus soluble receptor), presence of murine elements, and specificity of TNF-α blockade. Despite these distinguishing features, there does not seem to be a major difference in the efficacy of these 3 medications, with the important caveat that there have been few head-to-head comparisons. Selection of a particular agent is therefore more a function of physician and patient preferences and experience. One major side effect of this class is serious infections, particularly tuberculosis. Here, there does appear to be a notable difference in risk between particular anti–TNF-α agents, with etanercept apparently having a lower risk than adalimumab and infliximab.

Autoantibodies in the form of rheumatoid factor are present in most patients with RA. In the past, however, these antibodies were not thought to be pathogenic, which is one reason there was less focus on trying to understand the role of B cells in disease pathogenesis. In recent years, with elucidation of the importance of anticyclic citrullinated peptide antibodies as an early and specific diagnostic marker for RA,[8-9] and the perhaps somewhat surprising beneficial therapeutic effects of B-cell depletion, B cells have once again returned to center stage.

The B-cell–targeting agent currently approved for the treatment of RA is rituximab, which is a monoclonal antibody against CD20, a cell surface protein on B cells. Treatment with rituximab affects only cells that express this particular surface marker, which makes this drug a more targeted approach than non-specific cytotoxic chemotherapeutic agents. Monoclonal antibody technology can in this way be applied not only to specific cell types, but also to specific developmental stages in the life of these cells (ie, immature versus mature). The hope is that treatment with rituximab, and other "magic bullet" types of B-cell–targeted treatments already in development, will provide the maximum benefit possible from inhibiting this particular cell type, while minimizing the "collateral damage" observed with other, less-specific types of treatment.

Finally, Dr. Vibeke Strand reviews the clinical results of yet another novel and exciting approach recently approved by the US Food and Drug Administration for the treatment of RA: modulation of T-cell costimulation using abatacept (CTLA4-Ig, an engineered form of CTLA4 containing an Fc tail of an immunoglobulin molecule). In adaptive immune responses, T cells need to receive more than one signal for complete activation. What is known as "signal 1" is recognition by the T-cell receptor of the peptide/MHC complex on APCs, such as B cells and dendritic cells. "Signal 2" is generated by engagement of a specific ligand/receptor on APCs with their cognate receptor/ligand on T cells, otherwise known as costimulation. There are multiple pairs of costimulatory molecules, and more are being discovered. As Dr. Strand describes in her review, one important costimulatory pair is CD28 on T cells binding to CD80/86 on APCs. This is an activating signal, occurring early in the immune response. Later on, when the revved-up immune cells need to start winding down, an endogenous molecule called CTLA4 appears on the T cell, which also binds to CD 80/86 but transduces a negative (down-regulatory) signal. Abatacept binds to CD80/86, thus preventing the binding of CD28 and full T-cell activation.

In the treatment of RA, we are in the midst of what appears to be a success story, with the translation of exciting scientific discoveries into the day-to-day care of patients with previously unresponsive or partially responsive disease. As outlined by Drs. Kavanaugh, Markenson, and Strand, the treatment of RA is already very different and more effective than it was not long ago. From a disease for which clinicians had a limited number of therapeutic options, some of which were toxic or marginally effective, physicians now have at their disposal a number of approved medications targeting several different major components of the pathogenic cascade.

At present there are still many important questions to be answered: (1) What about long-term efficacy and safety? (2) Which patients benefit the most from particular BRMs? (3) Which particular combinations are safe and effective? (4) When are they most appropriate? The subsequent articles raise further questions. Nevertheless, these novel biologic agents clearly represent a major advance for patients with RA, particularly for those who could not tolerate or were less than optimally responsive to traditional medications. We hope to be able to continue the progress already made along the road to an actual cure for RA in the not-too-distant future.

AUTHOR'S DISCLOSURE STATEMENT

Dr. Putterman reports he has received grant/research support from Biogen Idec and is on the speakers' bureau of Bristol-Myers Squibb.

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