EDITORIALS

Kinase Inhibition — A New Approach to the Treatment of Rheumatoid Arthritis

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Two placebo-controlled trials reported in this issue of the *Journal* show the efficacy of an oral Janus kinase (JAK) inhibitor, tofacitinib, in the treatment of rheumatoid arthritis.[1,2] If this agent is approved by the Food and Drug Administration (FDA) for use in patients with rheumatoid arthritis, clinicians will confront several complex questions. What is the rationale for targeting this family of kinases? How effective is tofacitinib as compared with other proven agents that are used to treat rheumatoid arthritis? What safety concerns need to be kept in focus? How should JAK inhibition be combined with other medications in the management of rheumatoid arthritis? In addition, health systems will be interested in understanding the cost–benefit balance in the use of tofacitinib.

The JAK family includes four tyrosine kinases: JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2). These enzymes, which are expressed primarily in hematopoietic cell lineages, form part of the signaling apparatus used by receptors for various cytokines and growth factors. When such receptors are engaged by their specific ligands, JAKs phosphorylate and thus activate members of the signal transducer and activator of transcription (STAT) family. STATs 1 through 6 have specific and distinct effects on gene transcription in cells of the immune system that are critical in processes such as lymphocyte differentiation, immune regulation, and inflammation.[3] The importance of JAKs is emphasized by the delineation of profound immune deficiencies in the relatively few persons who have defects in the genes encoding JAK1 or JAK3.[4]

The compound now known as tofacitinib was first described in 2003 as a specific inhibitor of JAK3 that could prevent allograft rejection.[5] However, it is now considered to inhibit both JAK1 and JAK3 — two enzymes that can associate with the same cytokine receptors and function as signaling heterodimers. Tofacitinib is less active against JAK2, which associates primarily with growth factor receptors and which is therapeutically inhibited by ruxolitinib in the treatment of myelofibrosis.[6] Phase 3 clinical trials of tofacitinib for the treatment of rheumatoid arthritis in humans are based in part on beneficial effects of this JAK inhibitor in animal models of inflammatory arthritis[7,8] and in phase 2 studies involving patients with rheumatoid arthritis.[9,10]

Each of the trials reported in this issue of the *Journal* examined the use of tofacitinib (5 or 10 mg twice daily) in patients with rheumatoid arthritis whose disease was resistant to other disease-modifying drugs. Van Vollenhoven et al. added tofacitinib, adalimumab (an anti–tumor-necrosis-factor [TNF] antibody that is well established as a treatment for rheumatoid arthritis), or placebo to weekly methotrexate therapy in patients who had active disease despite methotrexate therapy. Fleischmann et al. enrolled patients who had not had a response to a variety of prior disease-modifying drugs — conventional, biologic, or both — and compared tofacitinib with placebo without the concurrent use of methotrexate or other disease-modifying drugs except hydroxychloroquine. The study design minimized the percentage of patients who received placebo and the length of time that these patients received the placebo. Both sets of investigators were successful in recruiting patients with very active rheumatoid arthritis and assessed the response to treatment using standard composite indexes of rheumatoid arthritis disease activity.

Over a 6-month period, clinically meaningful improvement was seen in the patients who received tofacitinib. In the von Vollenhoven trial,

the improvement was similar to the benefit with adalimumab. This study was not designed or powered to directly compare the efficacy of kinase inhibition with that of TNF blockade. The 6-month study period was sufficient to measure clinical responses, but radiographic end points, which are typically assessed at 1 to 2 years into a clinical trial, were not reported. The combination of methotrexate and a TNF inhibitor arrests the progression of radiographic damage in most patients with rheumatoid arthritis, and it will be important to determine whether the combination of methotrexate and tofacitinib is similarly effective.

In view of the critical roles of JAKs in signal transduction in immune responses and other physiologic processes, the potential toxic effects of a JAK1 and JAK3 inhibitor are a natural concern. Various adverse events were observed that are attributable to tofacitinib, including serious infections, such as tuberculosis. Other toxic effects included the elevation of hepatic aminotransferase levels, increased low-density lipoprotein cholesterol and high-density lipoprotein cholesterol levels, and neutropenia. This profile of adverse events is highly reminiscent of the pattern of toxic effects noted during treatment for rheumatoid arthritis with an anti–interleukin-6 receptor antibody, tocilizumab. The interleukin-6 receptor signals through a JAK–STAT mechanism, and actions of interleukin-6 are highly relevant to the pathogenesis of rheumatoid arthritis, as well as to a variety of metabolic processes. Thus, current data point to signaling components associated with the interleukin-6 receptor as a major mechanism for both the efficacy and the toxicity of tofacitinib,[10] but important effects of tofacitinib on other cytokine receptors would also be expected,[11] and tofacitinib could theoretically provide unique benefits and risks as compared with other treatments for rheumatoid arthritis.

The use of biologic agents to treat rheumatoid arthritis has occasionally been associated with the unexpected emergence of new autoimmune syndromes even as the rheumatoid arthritis responds to treatment. TNF inhibitors, for example, can induce lupus and demyelinating syndromes. Will similar events occur with JAK inhibition? One important consideration is that some of the cytokines that signal through JAK–STAT pathways, such as interleukin-4, can have antiinflammatory or immunoregulatory effects in many autoimmune conditions.[3,12] One report of the exacerbation by tofacitinib of autoimmune encephalomyelitis that had been experimentally induced in mice[13] suggests that clinical vigilance is appropriate and emphasizes that the clinical benefit of tofacitinib observed in patients with rheumatoid arthritis cannot be extrapolated to the expectation of a similar benefit in patients with other immune-mediated diseases without carefully controlled clinical trials.

The clear success of JAK inhibition as a treatment for rheumatoid arthritis, if confirmed by robust long-term efficacy assessed with the use of both clinical and radiographic measures, represents an important therapeutic advance. Considering that there are currently nine biologic medications (directed at five distinct molecular targets) that are FDA-approved for use in patients with rheumatoid arthritis, along with a range of effective conventional disease-modifying drugs that generally have good side-effect profiles,[14] the ideal clinical situations in which a kinase inhibitor should be used are not clear at present. A better understanding of the safety profile of tofacitinib will influence the consideration of when in the course of rheumatoid arthritis clinicians should consider this novel approach.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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DOI: 10.1056/NEJMe1206315

Pediatric Ventricular Assist Devices — First Steps for Babies

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Patients with severe cardiac failure who are candidates for heart transplantation may require temporary mechanical cardiac support to survive until a donor heart becomes available. This clinical observation is true of children as well as adults. Although the numbers of children may be much smaller than the numbers of adults thus affected, the potential number of years of life saved for each person is much greater for children.

Since the 1970s, the principal form of mechanical cardiac support for infants and children has been extracorporeal membrane oxygenation (ECMO). However, ECMO is designed for short-term support, and as waiting times for donor organs have grown progressively longer (especially for infants), the need for longer-term forms of support has become evident.

The development of ventricular assist devices for adults has been rapid over the past two decades. In contrast, the development of ventricular assist devices of appropriate size for children has been considerably slower. Nonetheless, it is clear that ventricular assist has advantages over ECMO in this population; in 2006, the Pediatric Heart Transplant Study Group reported an 86% rate of survival to transplantation in a group of 99 older children (median age, 13.3 years) who received a ventricular assist device,[1] a finding in stark contrast to the 39 to 75% survival rates among children receiving support with ECMO.[2,3]

In response to the need for better ventricular-assist options for young patients, the National Heart, Lung, and Blood Institute in 2004 awarded five contracts for the development of novel circulatory-support systems for use in small children.[4] These devices will soon be ready for clinical trials through the Pumps for Kids, Infants, and Neonates (PUMPKIN) program. In the meantime, the Berlin Heart Excor Pediatric ventricular assist device, designed for children with a body weight as low as 3 kg, was made available in the United States on a compassionate-use basis. Multiple single-institution reports, as well as the combined retrospective North American experience, have cited survival rates between 70 and 86% among patients receiving this device as a bridge to transplantation, which is substantially better than the rates cited in many reports on the use of ECMO.[5-8]

These successes set the stage for the first prospective multicenter study of pediatric ventricular assist devices to be performed in the United States, sponsored by the Food and Drug Administration (FDA) Office of Orphan Product Development. The outcomes in 48 children who prospectively received the Excor Pediatric ventricular assist device are presented by Fraser et al. in this issue of the *Journal*.[9] The children included in the trial were divided into two cohorts according to size; those in cohort 1 had a body-surface area of less than 0.7 m^2, and those in cohort 2 had a body-surface area of 0.7 to 1.5 m^2. The trial was designed to evaluate the safety and risk–benefit profile of this pump in both groups.

A randomized trial was not considered to be ethically feasible because of the mounting evidence of success with the device. Therefore, the decision was made to compare the prospective data with data from historical control groups of children who had received support with ECMO. The data on the patients in the ECMO control