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Editorial

The Clinical Efficacy of a JAK3-Selective Small Molecule Inhibitor, Tofacitinib, In Rheumatoid Arthritis

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Editorial

Rheumatoid arthritis RA) is an autoimmune disease characterized at the cellular level by the deregulated proliferation and phenotypic expression of activated immune cells and synoviocytes. In many RA patients, rheumatoid factor autoantibody and anti-cyclic citrullinated peptide antibody are present in serum. Within the milieu of inflammation of RA synovial joints, activated macrophages, T-cells, B-cells and neutrophils continuously migrate to, adhere and are retained in joint synovial tissue. The majority of cells within the RA synovium appear resistant to apoptosis by relevant cytokine/cytokine receptor interactions known to induce apoptosis in normal cells [1].

Inflamed RA synovial tissue produces pro-inflammatory cytokines at greatly elevated levels. These cytokines up-regulate matrix metalloproteinase (MMP) gene expression. In this regard activated MMPs mediate the degradation of articular cartilage extracellular matrix proteins resulting in cartilage destruction [2]. In addition, cytokine activation of receptor activator of nuclear factor-κB ligand/receptor activator of nuclear factor-κB/osteoprotegerin signaling leads to subchondral bone erosion via degradation of bone matrix proteins [3].

During the previous decade or so it was recognized that dampening the inflammatory response associated with the many cell types involved in the pathophysiologic response in RA would require a more thorough understanding of the signal transduction pathways that control the expression of cytokine, and chemokine genes, as well as those genes that regulate the expression of adhesion proteins [4]. During this period, it was also discovered that activation of the Janus Kinase/Signal Transducers and Activators of Transcription (JAK/STAT) pathway was largely responsible for perpetuating the chronic inflammatory state of RA by up-regulating pro-inflammatory cytokine gene expression [5].

It may be recalled that JAK Small Molecule Inhibitors (SMIs) were originally designed to suppress or even eliminate immune-mediated inflammation that accompanies organ transplant rejection. Thus, with this background in mind, a major effort was undertaken by a few biopharmaceutical companies to develop JAK SMIs that inhibit STAT protein phosphorylation (i.e. STAT activation) since it was conjectured that this mechanism would be pertinent to altering the expression of pro-inflammatory cytokines which are relevant for the medical therapy of RA.

Based on many pre-clinical analyses, it was anticipated that treatment of RA patients with a JAK3-selective SMI would have significant clinical efficacy. This was predicated on persuasive evidence that JAK3 was the only member of the JAK family that associates with a single cytokine-type receptor type, known as the "common γ-chain receptor." Thus, this receptor type regulates the downstream signaling initiated by many cytokines, including, interleukin-2 (IL-2), IL-4, IL-7, IL-9, IL-15, and IL-21, all of which are intimately involved in T-cell and natural killer cell activity, B-cell function and immune-cell proliferation [5,6]. Moreover, evidence accumulated during this period indicated that a JAK3-selective SMI, CP690,550, now known as tofacitinib, could also be clinically effective in RA via 1) the down-regulation of inflammation due to its capacity to suppress IL-17-mediated signaling 2) suppression of interferon-γ-production, 3) reduction in the deregulated proliferation of $CD4^+$ T-cells in inflamed RA synovium [7] and 4) suppression of the activation of the canonical JAK/STAT pathway initiated by the IL-6/IL6R/gp130 complex [5,8].

Following the mainly positive results of pre-clinical studies with JAK SMIs which showed that they could alter T-cell proliferation *in vitro* as well as the capacity of these JAK SMIs to ameliorate the severity of inflammatory arthritis in well-validated animal models of RA, clinical trials were begun in RA patients to determine the clinical efficacy of an orally-administered JAK3-selective SMI. Thus, tofacitinib was evaluated in RA patients. The results showed that tofacitinib exhibited demonstrable clinical efficacy with an acceptable safety profile in several RA clinical trials. The finding that tofacitinib was clinically efficacious in RA patients who had never been treated with Methotrexate (MTX) or who were non-responsive to treatment with MTX, other conventional Disease Modifying Anti-Rheumatic Drugs (DMARDs) or tumor necrosis factor-α (TNF-α) blockade was also noteworthy [7].

Overall and with few exceptions, the clinical data that emerged from several RA clinical trials testing the clinical efficacy of tofacitinib was impressive. Thus, a recent assessment of the results of 8 clinical studies, comprised of 4 Phase II and 4 Phase III trials in patients with active RA who had previously been found to be non-responders to conventional DMARDs, MTX or biologic drugs demonstrated a positive clinical response to tofacitinib. Furthermore, the results from the Phase III trials in which tofacitinib was compared to placebo, showed that tofacitinib significantly improved the American College of Rheumatology (ACR)-20 (ACR20) response, Health Assessment Questionnaire-Disability Index and ACR50 response after 3 months [9]. Most importantly, the clinical efficacy of tofacitinib was similar to those clinical responses achieved with the TNF inhibitor, adalimumab.

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However, the clinical efficacy of tofacitinib in these RA trials had to be considered against several common adverse events that occurred in the tofacitinib arm. These included, infections, infestations, increased creatinine, increased low-density-lipoprotein (LDL)-cholesterol/high density-lipoprotein (HDL)-cholesterol and decreased neutrophil counts [9].

In another RA clinical trial involving a comparator analysis of tofacitinib versus MTX [10] confirmed cases of cancer were observed, including 3 cases of lymphoma in 5 patients receiving tofacitinib and in 1 patient receiving MTX. Nevertheless, this most recent summary focusing on the clinical efficacy of tofacitinib in RA compared tofacitinib with MTX over the course of 24 months [10]. The results showed that the ACR70 response was greater in the tofactinib arm compared to the MTX group. However, the mean change in the modified total Sharp score (a measure of the progression of subchondral bone erosions) was modest in both the MTX and tofacitinib arms. In fact, the modified total Sharp score was significantly less in the tofacitinib group regardless of whether the 5mg or 10mg dose of tofacitinib was employed. Also noteworthy was the finding that patients in both tofacitinib dosage groups had less joint-space narrowing (a measure of articular cartilage loss) than patients in the MTX arm at 6, 12, and 24 months.

Approval of tofacitinib by the US Federal Drug Administration for the treatment of moderate-severe RA was achieved in 2012. At this juncture, tofacitinib appears to be most clinically useful in RA patients who have previously been treated with but who have had an inadequate clinical response to conventional DMARDs, biologic drugs, including anti-TNF blockade, anti-T-cell proliferation drugs and even rituximab, an inhibitor of B-cell proliferation. Thus, whether or not tofacitinib will ever be routinely employed as a first-line monotherapy in RA remains to be seen [11,12].

Importantly, the clinical effectiveness of tofacitinib for RA has spurred the development of and pre-clinical/clinical evaluation of additional JAK SMIs for RA and other autoimmune diseases, including baricitinib, decernotinib, filgotinib and INCB-039110 [13]. Thus, RA patients who were treated with baricitinib or INCB-039110 achieved acceptable ACR20 responses. Acceptable clinical efficacy was also reported with either the JAK1 SMI, filgotinib, or another JAK3 SMI, decernotinib. Tofacitinib has also been approved for treatment of psoriatic arthritis [14] an indication that this JAK3-selective SMI has clinical efficacy for other immune-cell mediated diseases besides RA.

Going forward it will be critical to assess the extent to which tofacitinib can be more routinely employed considering the clinical efficacy of JAK inhibitors in RA and whether or not chronic use of tofacitinib will result in serious adverse events that compromise patient safety. In addition, another important component of JAK-SMI therapy to be followed is the extent to which JAK2 inhibition [13] should be avoided and should not considered as a viable target for intervention in RA. Finally, the significant costs attributed to JAK SMIs, including tofacitinib must also be considered. It has been reported that the cost of tofacitinib exceeded $2,000 for a 30-day supply,

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