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Update on Safety Issues in the Treatment of Rheumatic Diseases

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Speakers from the Office of New Drugs, Center for Drug Development and Research, at the US Food and Drug Administration (FDA) provided updates for several commonly used rheumatic disease treatments.

Larissa Lapteva, MD, MHS, FDA, Silver Spring, Maryland, USA, reviewed two recently approved rheumatic disease treatments: prednisone delayed-release and tofacitinib. Prednisone delayed-release (approved July 2012) is available as 1-, 2-, or 5-mg tablets formulated with a prednisone-containing core tablet surrounded by an inactive outer shell that delays the onset of drug dissolution. Along with several nonrheumatic conditions, it is indicated as adjunctive therapy for short-term administration in acute gouty arthritis and during an exacerbation, or as maintenance therapy in selected cases of ankylosing spondylitis, dermatomyositis/polymyositis, polymyalgia rheumatica, psoriatic arthritis, relapsing polychondritis, rheumatoid arthritis (RA; including juvenile RA), Sjögren's syndrome, systemic lupus erythematosus (SLE), and vasculitis.

The median time to the peak plasma concentration with the delayed-release formulation is ~6 to 6.5 hours versus 2 hours with immediate-release prednisone. However, the similar peak plasma concentrations may only be achieved when the delayed-release formulation is given with food; when given under fasting conditions, the plasma concentration of the delayed-release formulation is lower than under fed conditions. The efficacy of the delayed-release formulation of prednisone in RA was assessed in one 12-week randomized controlled trial in adult patients with active RA. Participants (n=350) were randomly assigned to the delayed-release prednisone 5 mg or placebo QD in the evening in addition to their existing nonbiologic disease-modifying antirheumatic drug (DMARD) treatment. The primary study endpoint was the percentage of patients achieving a 20% improvement in RA signs and symptoms (ACR20 response) at Week 12.

When added to DMARD therapy, delayed-release prednisone was associated with significantly higher response rates versus placebo plus DMARD therapy on the ACR20 (47% vs 29%; 95% CI, 7.2 to 27.6) and ACR50 (22% vs 10%; 95% CI, 4.4 to 19.6). Delayed-release prednisone plus DMARD therapy was associated with a median decrease in morning stiffness of 55 minutes versus 33 minutes for placebo plus DMARD therapy. No new or unexpected safety concerns were raised during the clinical development program.

The Janus kinase (JAK) inhibitor tofacitinib (approved November 2012) is indicated either as monotherapy or in combination with methotrexate or other nonbiologic DMARDs in adult patients with moderately to severely active RA who have had an inadequate response or intolerance to methotrexate. It should not be used with biologic DMARDs or potent immunosuppressants such as azathioprine and cyclosporine. The approved dose is 5 mg BID. The effects of tofacitinib are primarily on JAK1 and JAK3, and, to a lesser extent, on JAK2 and tyrosine kinase 2.

The efficacy of tofacitinib was evaluated in 5 randomized, controlled trials (Table 1). In all studies, the ACR20/50/70 responses at 3 and 6 months were better for both doses of tofacitinib versus placebo; the between-dose difference was small. Treatment with tofacitinib also resulted in improved HAQ-DI scores. More patients achieved a score <2.6 on the 28-joint Disease Activity Score. Radiographic assessments suggested that tofacitinib may have an effect on radiographic progression, but the available data did not permit drawing definitive conclusions. The most common adverse events observed in the first 3 months of treatment with tofacitinib were diarrhea, nasopharyngitis, upper respiratory tract infection, headache, and hypertension.

Table 1. Tofacitinib Phase 3 Randomized Controlled Trials.*

Study	Design	Primary/ Secondary PEs	Timepoint	Publication
Patients with incomplete TNF response				
NCT00960440 (Trial 1032)	6 months background MTX	ACR20 HAQ-DI DAS28<2.6	Month 3 Month 3 Month 3	None
Patients with incomplete DMARD (MTX) response				
NCT00847613 (Trial 1044)	2 years background MTX	ACR20 mTSS HAQ-DI DAS28<2.6	Month 6 Month 6 Month 3 Month 6	None
NCT00856544 (Trial 1046)	1 year background DMARD	ACR20 HAQ-DI DAS28<2.6	Month 6 Month 3 Month 6	None
NCT00853385 (Trial 1064)	1 year background MTX adalimumab† or tofacitinib	ACR20 HAQ-DI DAS28<2.6	Month 6 Month 3 Month 6	van Vollenhoven RF et al. *N Engl J Med* 2012
NCT00814307 (Trial 1045)	6 months monotherapy	ACR20 HAQ-DI DAS28<2.6	Month 3 Month 3 Month 3	Fleischmann, R et al. *N Engl J Med* 2012

*All studies included a placebo arm; the doses of tofacitinib evaluated in each study were 5 and 10 mg BID. †40 mg once every 2 weeks. ACR20=American College of Rheumatology 20% improvement; DAS28=28-joint Disease Activity Score; DMARD=disease-modifying antirheumatic drug; HAQ-DI=Health Assessment Questionnaire-Disability Index; mTSS=modified Total Sharp Score; MTX=methotrexate; PE=primary endpoint; TNF=tumor necrosis factor.

The pooled safety analyses included data from the five Phase 3 trials and two Phase 2 trials, covering up to 12 months of exposure to tofacitnib. Data were analyzed for patients as treated after rescue or advancement from placebo to treatment groups. In these 7 controlled trials, malignancies were reported in 5 patients receiving tofacitinib 5 mg BID and in 7 patients receiving 10 mg BID, resulting in numerically higher exposure-adjusted incidence rates for malignancies in those receiving the 10-mg dose compared with the 5-mg dose. Serious infections reported with tofacitinib treatment included pneumonia, cellulitis, herpes zoster, and urinary tract infection; the overall exposure-adjusted incidence rates for serious infections were not numerically different between the 2 doses. Six cases of tuberculosis (TB) occurred in the randomized trials—all in patients receiving the 10-mg BID dose.

Hematologic abnormalities observed with tofacitinib treatment included dose-dependent decreases in neutrophil counts, initial occurrence of lymphocytosis followed by lymphopenia, and decreases in hemoglobin. In the overall development program, there were 15 cases of life-threatening lymphopenia, 11 of which were associated with infections. Patients treated with tofacitinib were observed to have small dose- and exposure-dependent elevations in serum creatinine. Elevated liver function tests were reported in ~20% of patients, mostly in those receiving concurrent DMARDs such as methotrexate. Tofacitinib was also associated with increases in low- and high-density lipoproteins but the low-/high-density lipoprotein ratio remained stable.

As recommended in tofacitinib's prescribing information, patients should be evaluated and tested for TB prior to using the drug and monitored throughout treatment. Blood counts should be taken at baseline, after 4 to 8 weeks, and every 3 months thereafter. Liver enzymes should be routinely monitored and lipid parameters assessed every 4 to 8 weeks. Tofacitinib therapy should be interrupted on occurrence of lymphopenia, neutropenia, anemia, or serious infection. The dose should be reduced to 5 mg daily in patients with moderate or severe renal insufficiency, moderate hepatic impairment, or when coadministered with potent inhibitors of cytochrome P-450 (CYP-450): CYP3A4 and CYP2C19 (eg, ketaconazole and fluconazole). Tofacitinib is not recommended for patients with severe hepatic impairment or baseline lymphopenia, neutropenia, or anemia.

Sally M. Seymour, MD, FDA, Silver Spring, Maryland, USA, reviewed several modifications to current warnings in existing labels. Pegloticase is a pegylated uric acid specific enzyme (biologic) approved for the treatment of chronic gout in patients refractory to conventional therapy. As a result of an increase in anaphylaxis and infusion reactions identified in clinical trials, pegloticase carries a boxed warning and is subject to a risk evaluation and mitigation strategy program. In April 2012, the pegloticase label was changed in response to postmarketing reports indicating that concomitant use of oral urate-lowering therapy and pegloticase may potentially blunt the rise of serum uric acid levels. The new labeling states that oral urate-lowering agents should be discontinued before starting pegloticase and oral urate-lowering therapy should not be initiated in patients being treated with pegloticase.

Belimumab is a B-lymphocyte stimulator inhibitor indicated for adult patients with active autoantibody-positive SLE receiving standard therapy. Hypersensitivity (including anaphylaxis) and infusion reactions during the clinical development program led to a warning in the label. Delayed (beyond 1 to 2 hours) hypersensitivity reactions noted in postmarketing reports and 1 patient death due to hypersensitivity led to a recent label update to include a warning on the potential for a delay in the onset of hypersensitivity and the potential for increased risk of hypersensitivity (possibly fatal) in patients with significant hypersensitivity or a history of multiple allergies.

Febuxostat is a xanthine oxidase inhibitor approved for the chronic management of hyperuricemia in patients with gout. When originally approved, the label contained a warning concerning liver enzyme elevations and recommended periodic assessment of liver function. A recent review of postmarketing reports, which showed hepatic failure (some fatal), jaundice, serious cases of abnormal liver function tests and liver disorder, led to an expanded hepatic effects warning being added to the label in November 2012. In addition to making clinicians aware of these reports, the new language recommends obtaining liver test panel at baseline and measurement of liver tests if patients have symptoms of liver injury (eg, fatigue, anorexia, right upper quadrant pain, or jaundice). Febuxostat should be stopped if alanine aminotransferase (ALT) level is >3 times upper-limit normal (ULN), and it should not be re-started unless an alternate explanation is identified. Febuxostat should also not be re-started in patients with ALT >3 times ULN and total bilirubin >2 times ULN without alternate etiology, as these patients are at risk for severe drug-induced liver injury.