EDITORIAL

Filgotinib, a JAK1 Inhibitor, for Treatment-Resistant Rheumatoid Arthritis

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Filgotinib is an oral, small-molecule inhibitor of Janus kinase (JAK)–signal transducer and activator of transcription, JAK1, one of the several subtypes of the enzyme.[1] Four JAKs exist in humans: JAK1, JAK2, JAK3, and nonreceptor tyrosine-protein kinase TYK2.[1,2] These kinases bind to types I and II cytokine receptors and transmit extracellular cytokine signals to activate various signal transducers and activators of transcription, which drive the proinflammatory machinery of the cellular immune response.[1] Two other JAK inhibitor drugs, tofacitinib[3] and baricitinib,[4] have been approved in the United States for the treatment of rheumatoid arthritis (RA). Tofacitinib preferentially inhibits JAK1, JAK3, and to a lesser extent JAK2.[1,2] Baricitinib inhibits JAK1 and JAK2.

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In a study in *JAMA*, Genovese et al[5] report findings from the first placebo-controlled, double-blind, phase 3 randomized clinical trial (RCT) of the JAK1 inhibitor filgotinib in treatment-refractory RA. A total of 449 patients with inadequate response or intolerance to at least 1 biologic disease-modifying antirheumatic drug (DMARD), and ongoing treatment with a conventional synthetic DMARD, were randomized to receive filgotinib, 200 mg; filgotinib, 100 mg; or placebo.

Filgotinib, 200 mg or 100 mg once daily, resulted in 34.9% and 26.4% more patients achieving an American College of Rheumatology 20% (ACR20) response (primary outcome) than placebo at 12 weeks (response rates for filgotinib, 200 mg, vs placebo were 66.0% vs 31.1% and for filgotinib, 100 mg, vs placebo were 57.5% vs 31.1%). Filgotinib was more effective than placebo for improvement in all secondary outcomes, including Health Assessment Questionnaire–Disability Index scores and 36-Item Short-Form Health Survey Physical Component summary score, the proportion achieving disease activity score in 28 joints using C-reactive protein of 3.2 or less, Functional Assessment of Chronic Illness Therapy–Fatigue scores, and ACR50 and ACR70 responses.

Nasopharyngitis, headache, and upper respiratory infections were the most common adverse effects. Four cases of herpes zoster and 1 retinal vein occlusion occurred among patients who received filgotinib.[5] Serious adverse events and infections occurred in 6 (4.1%) and 53 (36.1%) patients receiving filgotinib, 200 mg; 8 (5.2%) and 52 (34.0%) patients receiving filgotinib, 100 mg; and 5 (3.4%) and 38 (25.7%) patients receiving placebo, respectively. Two major cardiovascular adverse events were reported, 1 each in the filgotinib group and in the placebo group. There were no cases of opportunistic infection, active tuberculosis, malignancy, gastrointestinal perforation, or death. Filgotinib is not yet approved for use in the United States or other markets. Potential harms are always a concern with a new drug, and most current safety data for this drug class are from tofacitinib or baricitinib.

Serious adverse events are a concern with JAK inhibitor drugs. In a pooled analysis of phase 2 and phase 3 RCTs and long-term extension studies of tofacitinib up to March 2015, 6194 patients with a median exposure of 3.4 patient-years constituting 19 406 patient-years were analyzed.[6] The incidence rates (patients with events/100 patient-years) of serious adverse events were 9.4 (95% CI, 9.0-9.9); serious infections, 2.7 (95% CI, 2.5-3.0); herpes zoster, 3.9 (95% CI, 3.6-4.2); disseminated herpes zoster, 0.3 (95% CI, 0.2-0.4); opportunistic infections (excluding tuberculosis), 0.3 (95% CI, 0.2-0.4); and tuberculosis, 0.2 (95% CI, 0.1-0.3).[5] Overall, there is a similar risk of herpes zoster for both tofacitinib and baricitinib,[7,8] and this appears to be a drug class effect. In the study by Genovese et al,[5] the risk of herpes zoster with filgotinib was approximately 2.6/100 patient-years (4 cases in 300 patients over the 6-month study).

The risk of herpes zoster was higher with a higher tofacitinib dose (10 mg twice daily); with concomitant conventional DMARDs or glucocorticoids in trials[9]; and with glucocorticoids, but not with methotrexate (the most commonly used conventional DMARD) in a study population from clinical practice.[10] The risk of herpes zoster was increased with tofacitinib compared with abatacept (2.01 [95% CI, 1.40-2.88] in unadjusted analyses and 1.40 [95% CI, 1.09-1.81] in adjusted analyses) in another study of patients with RA treated in clinical practice settings.[11] Lower gastrointestinal tract perforation is another potential risk with tofacitinib[12] and potentially with baricitinib.[3,4] Similar to tofacitinib, risk of infection is evident with baricitinib.[13-15]

The 2 currently approved JAK inhibitor drugs for RA, tofacitinib and baricitinib, have black box warnings for serious infections and malignancies. Baricitinib carries a further caution of thrombosis.[4] Many hypotheses have emerged regarding whether and how the inhibition of JAK subtypes may impart different risks to these drugs, or differences in relative efficacy, but these issues remain unresolved. Some laboratory effects, including a reduction in lymphocytes, NK cells, and neutrophils, may be consistent with the biological differences in JAK subtype inhibition. Correlating JAK subtype inhibition with specific harms, such as thrombosis, herpes zoster, and other risks, is challenging at present. Mechanistic and large postmarketing clinical studies of each agent are needed to better understand these potential harms and adverse events

and the subpopulations of patients with RA at highest risk of specific harms, considering their comorbidity profile and concomitant medications.

In the study by Genovese et al,[5] the authors appropriately acknowledge that this short-duration efficacy study cannot definitively determine the harms related to filgotinib or its long-term efficacy. Data from additional randomized trials in RA are currently underway (NCT01888874, NCT01894516, NCT02889796, NCT02886728) and large postmarketing surveillance studies will clarify the potential harms and risks with filgotinib, as well as assess whether the adverse event profile of this drug differs from that of tofacitinib or baricitinib.

While the authors described the frequency of laboratory abnormalities, including elevations in creatinine, creatine kinase, and liver function tests, in the group treated with filgotinib, 200 mg, to be of similar frequency compared with the placebo group, a rate of 25.9% vs 12.2% for elevated aspartate aminotransferase may not be similar. No clinical liver toxicity was evident; therefore, the clinical relevance of this difference cannot be determined. This may be relevant in the future, once the drug is approved for use, especially for use in patients with liver disease, including hepatitis and alcoholic liver disease.

The muscle enzyme, creatine kinase, was elevated in 29.3% of the patients treated with filgotinib, 200 mg, vs 10.8% of placebo-treated patients. Most creatine kinase elevations were transient, with only a few patients with grade 3 or higher abnormality, in the absence of muscle disease. The absence of clinical signs and symptoms is reassuring. What is the clinical relevance of the dose effect evident for these laboratory abnormalities between the 100-mg and 200-mg filgotinib doses? Will that translate into frequent laboratory test monitoring, increased rates of clinical events, or both in larger postmarketing surveillance studies? Further insights into medication-specific and drug class–specific harms of JAK inhibitors are needed. The regulatory agencies will certainly assess whether some of these are dose-related adverse events during the evaluation of the drug for potential approval. Cumulative data from multiple RCTs will make these assessments possible. Comparative studies of tolerability of filgotinib and other JAK inhibitors are also needed to better understand what propotion of people with RA will continue these medications intermediate- and long-term.

The 2015 ACR guideline for the treatment of RA recommends the use of triple traditional DMARD therapy, addition or substitution with tumor necrosis factor biologic, nonbiologic, or oral JAK inhibitor in cases of inadequate response to conventional DMARD monotherapy (most often methotrexate).[16] The approval of baricitinib for RA since the publication of the ACR RA guideline has expanded the treatment options. The potential availability of other JAK inhibitor drugs, such as filgotinib, peficitinib, and upadacitinib, in the future will further expand the choices within this class of medications. As with all new therapies, the balance of benefits and risks needs to be well established in phase 3 studies before regulatory approval. The oral route of administration of JAK inhibitors is more convenient than injectable biologics for some patients with RA. However, the risk profile of filgotinib and other JAK inhibitors is more similar to the biologic DMARDs rather than the conventional DMARDs, such as methotrexate, with comparable risks of serious infections, herpes zoster, and opportunistic infections.

In conclusion, the trial by Genovese et al[5] provides pivotal data on the efficacy of filgotinib, a JAK1 selective inhibitor, in RA refractory to biologic DMARDs. Having more viable treatment options for refractory RA is highly desirable. RA is a heterogeneous disease, and a significant proportion of patients with RA are either nonresponders or are intolerant to all current therapies. However, to help promote use, these oral JAK inhibitor therapies will need to be priced at levels comparable with the conventional synthetic DMARDs rather than the biologics. Patients and clinicians express frustration over the high pricing of new RA therapies because a portion of the cost is often passed on to the patients by the health insurance plan, which limits access to these therapies. Head-to-head comparison of filgotinib with other JAK inhibitors, biologic DMARDs, and triple conventional DMARD therapy will further define the most appropriate use of filgotinib for patients with RA by examining the comparative efficacy and safety.

ARTICLE INFORMATION

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Conflict of Interest Disclosures: Dr Singh reported receiving personal fees from Horizon, Medisys, Fidia, UBM LLC, Medscape, WebMD, Clinical Care Options, ClearView Healthcare Partners, Putnam Associates, Spherix, the National Institutes of Health, and the American College of Rheumatology (ACR); owning stock options in Amarin Pharmaceuticals and Viking Therapeutics; and serving on the OMERACT executive board, the Food and Drug Administration advisory committee, and the Veterans Affairs Rheumatology Field Advisory Committee. He is the editor and director of the UAB Cochrane Musculoskeletal Group Satellite Center on Network Meta-analysis and previously served on the following committees: member, the ACR's annual meeting planning committee and quality of care committees; chair, ACR Meet-the-Professor and workshop and study group subcommittee; and co-chair, ACR criteria and response criteria subcommittee.

Funding/Support: Dr Singh is supported by the resources and the use of facilities at the VA Medical Center at Birmingham, Alabama.

Role of the Funder/Sponsor: The funder had no role in the preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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