Janus Kinase Inhibitors for the Treatment of Rheumatoid Arthritis

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Abstract

Rheumatoid arthritis (RA) is a disease where the immune system attacks the linings of the joints, resulting in joint pain, stiffness, swelling, and destruction. Although many products are available for the treatment of RA, limitations such as adverse reactions and tolerance greatly affect adherence. Many of the current biologic disease-modifying antirheumatic drugs on the market are injectables, leaving a void to be filled for a product that can be taken orally. The most advanced of these approaches, the Janus kinase (JAK) inhibitors, are oral drugs that have not only made a breakthrough in RA, but also other skin conditions.

Keywords

intravenous therapy, formulary management/P&T, rheumatology

Epidemiology

Rheumatoid arthritis (RA) is the most common autoimmune inflammatory arthritis in adults. The prevalence is 1% to 2% of the adult population (0.3% of patients <35 years old and 10% of those >65 years old).¹ The usual age of onset for RA is between 30 and 50 years. Rheumatoid arthritis affects 3 to 5 times more women than men. Prevalence does not increase with age. It affects approximately 1.3 million people in the United States. It is estimated that the direct health care costs, as well as the consequential costs of RA in the United States, are more than \$19 billion annually. Conventional disease-modifying antirheumatic drugs (DMARDs) are small molecules and inexpensive. They are much more affordable today than they were several years ago. Most patients can expect to pay between \$1500 and \$2000 annually for conventional DMARD medications. These costs will vary by the type and brand of medication. Biologics have a monthly cost that ranges from \$1300 to \$3000. Biologics may cost the patient well over \$30 000 annually without health insurance or financial assistance.²

Current Treatment

There are a few different approaches when considering pharmacologic therapy in treating RA. Current American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) guidelines recommend initiating treatment with conventional DMARDs in patients with RA. Methotrexate is the preferred DMARD to initiate in a new patient. If disease activity is not decreased, then adding a second DMARD or switching to a biologic DMARD with or without methotrexate is recommended.

Many biologics are available for the treatment of RA. These include tumor necrosis factor inhibitors (TNFi), abatacept, and the interleukin-6 receptor-alpha inhibitor, tocilizumab. Under certain circumstances, rituximab is also used. Evidence is lacking regarding which biologics should be used in and in what sequence. Most biologic DMARDs are given by injection or infusion. Both traditional DMARDs and biologics can increase the patient's risk for infection, especially the increased risk for pneumonia with biologics. Another problem is that not all available DMARDs, whether traditional or biologic, prevent progressive joint damage, and they do not always significantly improve quality of life.³

New Treatment Options

Janus kinase (JAK) inhibitors are in the nonreceptor tyrosine kinase family, which play a pivotal role in the pathological processes of RA. Several JAK inhibitors have been developed as new therapies for patients with RA. These are all oral biologic DMARDs that inhibit JAK 1, 2, and 3. One JAK inhibitor, tofacitinib, has already been approved. Results of Phase III clinical trials using the JAK 1, 2 inhibitor, baricitinib, have shown promise. Both drugs are effective in patients who showed inadequate response to biological DMARDs as well

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Table 1. Janus Kinase Inhibitors.

Generic name	Sponsor	JAK inhibition	Comments
Tofacitinib	Pfizer Inc	JAK 1, 2, 3 inhibitor	Approved for use in rheumatoid arthritis. In the Phase III Oral-Sync trial, tofacitinib demonstrated improvements in PtGA, Pain, HAQ DI, all 8 SF-36 domains, FACIT-F, and MOS Sleep at 3 months. ⁴
Baricitinib	Eli Lilly and Company; Incyte Corporation	JAK 1, 2 inhibitor	An NDA was submitted in January 2016, but review has been delayed pending submission of additional clinical data on safety and dosing. Baricitinib is approved in Europe for RA. In a trial of 684 rheumatoid arthritis patients who had had an inadequate response to methotrexate, 62% of patients treated with baricitinib achieved ACR20 response at week 52 compared with 39%, with placebo. ⁵
Filgotinib	Galapagos NV; Gilead Sciences	JAK 1 inhibitor	In the 12-week, 594 rheumatoid arthritis patient, dose ranging, Phase II DARWIN-1 trial, 69-74% of filgotinib treated patients achieved an ACR20 response compared with 44%, with placebo. ⁶
Upadacitinib	AbbVie Inc	JAK 1 inhibitor	Topline results were announced for SELECT-NEXT, a 662 patient, Phase III trial in patients with moderate-to-severe RA. Upadacitinib doses demonstrated ACR20 response rates of 64%, and 66% in the 15 mg and 30 mg compared with 36% in the placebo group at 12 weeks.

Source. Information adapted from the Prescribe Right Pharmaceutical Pipeline Tracker database.⁷

Note. JAK = Janus kinase; ORAL-Sync = Oral Rheumatoid Arthritis Phase 3 Trials–Synchronized; PtGA = Patient Global Assessment; HAQ DI = Health Assessment Questionnaire–Disability Index; SF-36 = Short Form Health Survey; FACIT-F = Functional Assessment of Chronic Illness Therapy–Fatigue; MOS = Medical Outcome Study; NDA = New Drug Application; RA = rheumatoid arthritis; ACR20 = American College of Rheumatology 20% response rate.

as traditional DMARDs. In addition, Phase III trials using filgotinib and upadacitinib, specific JAK 1 inhibitors, are currently underway. JAK inhibitors are novel therapies for RA, but further studies are needed to determine their risk-benefit ratio and selection of the most appropriate patients for such therapy.⁴ The cost of JAK inhibitors per year average around the same price as a TNFi. Drug administration time and convenience are greatly saved with JAK inhibitors because of the oral administration. Due to the promising findings of JAK Inhibitors, they are expected to represent the next generation compounds for treating RA.

Authors' Note

Information is summarized from selected materials; additional information may be available from other sources. Due to the preapproval nature of the information, non-peer-reviewed data may be utilized. The information provided is meant to provide a way to assess the development status of a new drug and should not be used in making patient care decisions.

Declaration of Conflicts of Interest

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