Rheumatoid arthritis (RA), a chronic, inflammatory autoimmune disorder, affects approximately 1.5 million individuals in the United States; it is 3 times more common in women than in men. RA affects the lining or synovium of the joints, causing painful swelling that can lead to bone erosion and deformity. RA can affect other organs, including skin, eyes, heart, lungs, and blood vessels. Patients with RA are also at increased risk for cardiovascular disease.

RA imposes a substantial clinical burden on patients, affecting their physical function and quality of life, including daily activity, sleep, and mental health. The treatment of RA is focused on eliminating inflammation, preventing joint and organ damage, and improving physical function. The American College of Rheumatology (ACR) practice guidelines recommend a treat-to-target approach to achieve remission or low disease activity for early and advanced disease. Pharmacologic treatments include nonsteroidal anti-inflammatory drugs (NSAIDs), steroids, traditional disease-modifying antirheumatic drugs (DMARDs), and biologic response modifiers, a newer class of DMARDs.

**FDA Approves Sarilumab for Rheumatoid Arthritis**

On May 22, 2017, the US Food and Drug Administration (FDA) approved sarilumab (Kevzara; sanofi-aventis/Regeneron), an interleukin (IL)-6 receptor antagonist, for the treatment of adults with moderately to severely active RA who cannot tolerate or have had an inadequate response to ≥1 DMARDs.

“Sarilumab demonstrated statistically significant, clinically-meaningful improvements in adult patients with rheumatoid arthritis,” said Alan Kivitz, MD, CPI, Medical Director, Altoona Arthritis and Osteoporosis Center.

**Mechanism of Action**

Sarilumab is a human recombinant monoclonal antibody that binds to IL-6 receptors that inhibit IL-6-mediated signaling. The IL-6 cytokine plays a role in the body’s inflammatory process and response. The production of IL-6 by synovial and endothelial cells can lead to local production of IL-6 in the joints affected by RA and other inflammatory processes. Elevated levels of IL-6 have been correlated with disease activity and joint damage in patients with RA.

**Dosing and Administration**

The recommended dosage of sarilumab is 200 mg once every 2 weeks, administered as a subcutaneous injection; it is available as a 150-mg/1.14-mL or 200-mg/1.14-mL solution in a single-dose, prefilled syringe, and can be used as monotherapy or in combination with methotrexate or other conventional DMARDs.

Treatment should not be initiated in patients with an absolute neutrophil count (ANC) <2000/mm³, platelets <150,000/mm³, or liver transaminase levels above 1.5 times the upper limit of normal. Dose modifications are recommended in cases of neutropenia, thrombocytopenia, and/or elevated liver transaminase levels.

**Pivotal Phase 3 Clinical Trials**

The FDA approval of sarilumab was based on the data from 2 phase 3 clinical trials in adults with moderately to severely active RA. MOBILITY included 1197 patients with inadequate response to methotrexate. Patients were randomized to sarilumab 150 mg, 200 mg, or placebo every 2 weeks, with methotrexate. After week 16, patients with inadequate response were eligible for rescue treatment with sarilumab 200 mg every 2 weeks. Sarilumab plus methotrexate showed significant improvements in ACR 20% response improvement (ACR20) score at week 24, in Health Assessment Questionnaire-Disability Index (HAQ-DI) at week 16, and in van der Heijde–modified Total Sharp Score radiographic changes at week 52 versus placebo plus methotrexate (P <.0001 for all; Table).

TARGET included 546 patients with moderate-to-severe RA who had an inadequate response or were intolerant to ≥1 tumor necrosis factor-α antagonists. Patients received sarilumab 150 mg, sarilumab 200 mg, or placebo every 2 weeks with concomitant DMARDs. After week 12, patients with an inadequate response were eligible to receive rescue therapy with sarilumab 200 mg every 2 weeks.

At week 24, sarilumab plus DMARDs significantly improved ACR20 score versus placebo. In addition, the 2...
sarilumab groups showed significant improvements from baseline in HAQ-DI score at 12 weeks versus placebo.\textsuperscript{11,14}

Adverse Reactions

The most common (incidence \(\geq 3\%\)) adverse reactions associated with sarilumab therapy are neutropenia (7\%), increased alanine aminotransferase levels (5\%), injection-site erythema (5\%), upper respiratory infections (4\%), and urinary tract infections (3\%).\textsuperscript{11}

Contraindications

Sarilumab is contraindicated in patients with a hypersensitivity to sarilumab or to any of its inactive ingredients.\textsuperscript{11}

Drug Interactions

Cytokines and cytokine modulators can influence the activity of specific cytochrome (CY) P450 enzymes (including CYP3A4) and thus may alter the metabolism of drugs that are substrates of these enzymes. Use caution when sarilumab is co-administered with CYP3A4 substrate drugs for which decreased effectiveness is undesirable (eg, oral contraceptives, statins).\textsuperscript{11}

Use in Specific Populations

Nursing women may need to discontinue sarilumab or discontinue nursing.\textsuperscript{11}

No differences in safety or efficacy of sarilumab were seen between older (aged \(\geq 65\) years) and younger patients.\textsuperscript{11}

Warnings and Precautions

The prescribing information for sarilumab includes a boxed warning stating that sarilumab is associated with an increased risk for serious and potentially fatal infections, including bacterial, viral, invasive fungal, and other opportunistic infections. Patients should be monitored closely for infection while receiving sarilumab.\textsuperscript{11}

Sarilumab has been associated with reduced ANC, including neutropenia; a reduction in platelet counts; transaminase elevations; and lipid abnormalities.\textsuperscript{11}

The risk for gastrointestinal perforation may be increased when sarilumab is used concomitantly with NSAIDs or with corticosteroids.\textsuperscript{11}

Treatment with immunosuppressant drugs, including sarilumab, may increase the risk for malignancies.\textsuperscript{11}

Sarilumab should be discontinued immediately if anaphylaxis or a hypersensitivity reaction occurs.\textsuperscript{11}

Sarilumab should not be used with live vaccines.\textsuperscript{11}

Conclusion

The FDA approval of sarilumab represents a new treatment option for patients with moderate-to-severe RA who have had an inadequate response or intolerance to \(\geq 1\) DMARDs. Sarilumab plus methotrexate and sarilumab plus DMARDs significantly improved outcomes in patients with RA.\textsuperscript{11}

<table>
<thead>
<tr>
<th>Table</th>
<th>MOBILITY: Sarilumab plus Methotrexate versus Placebo plus Methotrexate in Moderate-to-Severe Rheumatoid Arthritis</th>
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</thead>
<tbody>
<tr>
<td>Co-primary end points</td>
<td>Sarilumab 150 mg + methotrexate (N = 400)</td>
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<tr>
<td>ACR20</td>
<td></td>
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<tr>
<td>Week 24, %</td>
<td>58.0</td>
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<tr>
<td>Difference from placebo, %</td>
<td>24.6 (95% CI, 18.8-31.3)</td>
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<tr>
<td>HAQ-DI</td>
<td></td>
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<tr>
<td>Change from baseline at week 16</td>
<td>−0.54</td>
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<tr>
<td>Difference from placebo at week 16</td>
<td>−0.24 (95% CI, 0.31 to −0.16)</td>
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<tr>
<td>Patients with clinically meaningful improvement, %</td>
<td>53.8</td>
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</tbody>
</table>

\(\textsuperscript{a}\)Patients who were rescued or discontinued were deemed nonresponders for the analyses; at week 52, 270 patients continued sarilumab 150 or 200 mg, and 196 continued to receive placebo. ACR20 indicates American College of Rheumatology 20\% response improvement; CI, confidence interval; HAQ-DI, Health Assessment Questionnaire Disability Index; NA, not applicable.


References