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New Disease-Modifying Anti-Rheumatic Drugs for Management of Rheumatoid Arthritis

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Rheumatoid arthritis (RA) is an autoimmune inflammatory disease that causes cartilage damage, bone erosions, and eventually joint deformity.[1] Inflammation in RA is mediated by activation of T-cells, B-cells and macrophages which leads to expression of cytokines such as tumor necrosis factor (TNF) and interleukins (IL).[1] Biologic or Targeted Synthetic Disease-Modifying Anti-Rheumatic Drugs (bDMARDs or tsDMARDs) are recommended for patients with a suboptimal response or intolerance to Conventional Synthetic Disease-Modifying Anti-Rheumatic drugs (csDMARDs), such as methotrexate (MTX), sulfasalazine, hydroxychloroquine or leflunomide **(Table1)**.[2,3] Biosimilar agents are available for adalimumab, infliximab and etanercept. The purpose of this newsletter is to review the efficacy and safety for 3 recently approved DMARDs to manage RA: sarilumab, baricitinib, and upadacitinib.

Table 1. FDA-approved bDMARDs and tsDMARDs to Manage RA[4,5]

Drug - Route of Administration	Molecular Target
Biologic Disease-Modifying Antirheumatic Drugs (bDMARDs)	
Adalimumab – SC (HUMIRA)	TNF
Certolizumab Pegol – SC (CIMZIA)	
Etanercept – SC (ENBREL)	
Golimumab - IV or SC (SIMPONI and SIMPONIARIA)	
Infliximab – IV (REMICADE)	
Sarilumab – SC (KEVZARA)	IL-6 Receptor
Tocilizumab – IV or SC (ACTEMRA)	
Anakinra – SC (KINERET)	IL-1
Rituximab – IV (RITUXAN)	B-lymphocyte
Abatacept - IV or SC (ORENCIA)	T-lymphocyte
Targeted Synthetic Disease-Modifying Antirheumatic Drugs (tsDMARDs)	
Tofacitinib – PO (XELJANZ)	JAK 1,2,3
Baricitinib – PO (OLUMIANT)	JAK 1,2
Upadacitinib – PO (RINVOQ)	JAK 1
Abbreviations: FDA=Food and Drug Administration; IL=interleukin; IV = intravenous; JAK=Janus kinase; PO=oral; RA =rheumatoid arthritis; SC = subcutaneous; TIM=targeted immune therapy; TNF = tumor necrosis factor	

Assessment of Efficacy for Rheumatoid Arthritis Therapies

Primary endpoints frequently studied in clinical trials for RA therapies include the American College of Rheumatology (ACR) response and the 28-joint Disease Activity Score (DAS-28). The ACR20 is a composite measure defined as a 20% improvement in the number of tender and swollen joints, and a 20% improvement in 3 of the following 5 criteria: patient global assessment, physician global assessment, visual analog pain scale, patient assessment of physical functioning, and either erythrocyte sedimentation rate (ESR) or c-reactive protein (CRP).[6] ACR50 and ACR70 criteria are similar, but with improvement of at least 50% and 70% in ACR criteria, respectively.[6] The DAS-28 is another index of disease activity. The DAS-28 is a composite outcome that consists of: 1) the number of painful joints; 2) number of swollen joints; 3) ESR or CRP and 4) patient assessment of disease activity.[7] A DAS-28 score greater than 5.1 corresponds to high disease activity and a score of less than 3.2 corresponds to low disease activity.[7]

Sarilumab: IL-6 Receptor Inhibitor

Sarilumab and tocilizumab bind to IL-6 receptors which inhibits IL-6 mediated signaling. Tocilizumab binds to the entire IL-6 receptor, while sarilumab targets the alpha subunit of the receptor.[8] Sarilumab is approved for the treatment of adult patients with moderate-to-severe RA who have had an inadequate response to one or more DMARDs.[9] Sarilumab may be used as monotherapy or in combination with other csDMARDs. The recommended dose is 200 mg subcutaneously every 2 weeks. The dose should be reduced to 150 mg in patients with neutropenia, thrombocytopenia, or elevated liver enzymes.[9] The Food and Drug Administration (FDA) approval was based on 3 randomized clinical trials (RCTs) in which efficacy and safety of sarilumab was compared to placebo or adalimumab.[10-12] Details of each study are provided in **Table 2**.

Table 2. Clinical Trial Data for Sarilumab

Trial Name	Comparators	ACR 20 Response at Week 24	ARR/NNT
MOBILITY B[10] n=1,197	SARI 150 mg vs. PBO SARI 300 mg vs. PBO	ACR20: 58% vs. 22% ACR20: 66% vs. 22%	36%/3 44%/3 P<0.0001 for both 95% CI NR
TARGET[11] n=546	SARI 150 mg vs. PBO SARI 300 mg vs. PBO	ACR20: 56% vs. 34% ACR20: 61% vs. 34%	22%/5 27%/4 P<0.0001 for both 95% CI NR
MONARCH[12] n=346	SARI 200 mg vs. ADA 40 mg every 2 weeks	72% 59%	13%/8 P<0.0074 95% CI NR
Abbreviations: ACR= American College of Rheumatology; ADA=adalimumab; ARR=absolute risk reduction; CI=confidence interval; NNT=number needed to treat; NR=not reported; PBO=placebo; SARI=sarilumab			

Similar to other DMARDs, sarilumab includes an FDA black boxed warning for risk of serious infections.[9] Labeling for sarilumab also has warnings for neutropenia, thrombocytopenia, elevated liver enzymes, lipid abnormalities, gastrointestinal perforation, hypersensitivity, and co-administration with live vaccines.[9] These warnings are similar to those for tocilizumab.

Baricitinib and Upadacitinib: JAK inhibitors

JAK inhibitors are among the newest class of treatments for RA. JAK proteins are implicated in the pathogenesis of RA as they play an important role in the signalling pathways of various cytokines, growth factors, and hormones involved in immunity and hematopoiesis.[13] Three JAK inhibitors (tofacitinib, baricitinib, and upadacitinib) have been approved and each has a different inhibitory profile for the JAK proteins (see **Table 1**). JAK inhibitors are potent immunosuppressants. There are a number of well-known safety issues associated with use of this class of medications, including serious infections, malignancy, lymphoproliferative disorders, gastrointestinal perforations, lymphopenia, neutropenia, anemia, and lipid elevations.[14] Based upon accumulating data regarding the risk of thrombosis with JAK inhibitors, thrombosis is now also considered a class safety issue for JAK inhibitors.[15]

Baricitinib is an oral JAK inhibitor approved for treatment of adult patients with moderate-to-severe RA who have had an inadequate response to one or more TNF inhibitor (TNFi) therapies.[16] The recommended daily dose is 2 mg once a day as monotherapy or in combination with MTX.[16] The efficacy and safety of baricitinib was assessed in 4 phase 3 RCTs.[17-20] Baricitinib 2 and 4 mg doses were compared to placebo in adults with RA who had an inadequate response to MTX (RA-BEAM), an inadequate response to csDMARDs (RA-BUILD), and in patients refractory to TNFis (RA-BEACON).[13] In all trials except for RA-BEGIN, patients continued background MTX therapy. Results of the primary endpoint in these trials, ACR20 response at week 12 or 24, are summarized in **Table 3.** In the 3 placebo-controlled trials, baricitinib was superior to placebo in achieving ACR20 response. In RA-BEAM, baricitinib was compared to adalimumab as noninferiority endpoint (estimated power for test of noninferiority, 93%; prespecified noninferiority margin of 12%).[18] Baricitinib was found to be noninferior to adalimumab at week 12 for the ACR20 response.[18] According to the pre-specified statistical analysis plan, baricitinib was also considered to be superior to adalimumab based on ACR20 response at 12 weeks (P≤0.05).[18]

Table 3. Clinical Trial Data for Baricitinib

Trial Name	Comparators	ACR 20 Response at Week 12	ARR/NNT
RA-BEGIN[17] n=588	BARI 4 mg daily vs. oral MTX weekly	77% vs. 62%* *Week 24	15%/7 95% CI NR; P≤0.05
RA-BEAM[18] n=1,307	BARI 4 mg daily vs. PBO BARI 4 mg daily vs. ADA 40 mg every other week	70% vs. 40% 70% vs. 61%	30%/4 95% CI NR; p≤0.001 9%/12 95% CI NR; P≤0.05
RA-BUILD[19] n=684	BARI 2 mg daily vs. PBO BARI 4 mg daily vs. PBO	66% vs. 39% 62% vs. 39%	27%/4 95% CI NR; P≤0.001 23%/5 95% CI NR; P≤0.001
RA-BEACON[20] n=527	BARI 2 mg daily vs. PBO BARI 4 mg daily vs. PBO	49% vs. 27% 55% vs. 27%	22%/5 95% CI NR; P<0.001 28%/4 95% CI NR; P<0.001

Abbreviations: ACR=American College of Rheumatology; ADA=adalimumab; ARR=absolute risk reduction; BARI=baricitinib; CI=confidence interval; MTX=methotrexate; NNT=number needed to treat; NR=not reported; PBO=Placebo

The most common adverse effects noted in clinical trials with baricitinib 2 mg and 4 mg were upper respiratory tract infections (14-16%), nausea (3%), and herpes infections (0.8-1.8%).[16] There is insufficient evidence to determine differences in long-term efficacy, long-term safety, remission rates, health-related quality of life, or functional improvement with baricitinib compared to other treatments for moderate-to-severe RA.

Upadacitinib is an oral selective JAK-1 inhibitor indicated for the treatment of adults with moderate-to-severe RA who have had an inadequate response or intolerance to MTX.[21]. Approval of upadacitinib was based on 4 phase 3 RCTs conducted in adults with moderate-to-severe RA.[22-25] The SELECT-NEXT and SELECT-COMPARE trials included adults with an inadequate response to csDMARDs. The SELECT-BEYOND trial included patients with an inadequate response to bDMARDs. Background csDMARDs were continued in all of the placebo-controlled trials. Two doses of upadacitinib (15 mg and 30 mg once daily) were studied in the trials; however due to safety concerns with the 30 mg dose (e.g. anemia, neutropenia), only the 15 mg dose was approved. The SELECT-COMPARE trial was also designed to test for the noninferiority and superiority of upadacitinib to adalimumab. Results for the trials are summarized in **Table 4.**

Table 4. Clinical Trial Data for Upadacitinib

Trial Name	Comparators	ACR 20 at week 12	ARR/NNT
SELECT-MONOTHERAPY[22] n=648	UPA 15 mg daily vs. oral MTX weekly UPA 30 mg daily vs. oral MTX weekly	68% vs. 41% 71% vs. 41%	27%/4 95% CI 18 to 36 p≤0.0001 30%/4 95% CI 21 to 39 p≤0.0001
SELECT-NEXT[23] n=661	UPA 15 mg daily vs. PBO UPA 30 mg daily vs. PBO	64% vs. 36% 66% vs. 36%	28%/4 95% CI 19 to 37 p<0.0001 30%/4 95% CI 22 to 39 p<0.0001
SELECT-COMPARE[24] n=1,629	UPA 15 mg daily vs. PBO UPA 15 mg daily vs. ADA 40 mg every other week	71% vs. 36% 63% vs. 36%	34%/3 95% CI 29 to 39 p≤0.001 8%/13 95% CI, 1 to 14 p≤0.05
SELECT-BEYOND[25] n=499	UPA 15 mg daily vs. PBO UPA 30 mg daily vs. PBO	65% vs. 28% 56% vs. 28%	37%/3 95% CI 26 to 46 p<0.0001 28%/4 95% CI 18 to 38 P<0.0001

Abbreviations: ACR=American College of Rheumatology; ADA=adalimumab; ARR=absolute risk reduction; CI=confidence interval; MTX= methotrexate; NNT=number needed to treat; NR=not reported; PBO=Placebo; UPA=upadacitinib

Reported safety data from these trials demonstrated that patients treated with upadacitinib 15 mg experienced greater frequency of adverse events compared to placebo, including upper respiratory infection, nausea, cough, and pyrexia.[21] Upadacitinib and baricitinib prescribing information contains FDA black boxed warnings for serious infections leading to hospitalization or death, risk of lymphoma, and fatal thrombosis associated with JAK inhibitor administration.[16,21] Upadacitinib and baricitinib are not recommended for use in combination with other JAK inhibitors, bDMARDs, or with immunosuppressants such as azathioprine or cyclosporine.[16, 21]

In the Medicaid Fee-For-Service population, adalimumab and etanercept are preferred agents. All of the biologic agents require prior authorization to ensure safe and appropriate use.

Conclusions

Three DMARDs recently received FDA-approval to manage moderate-to-severe RA in adults who have had an inadequate response to MTX or other DMARDs. Sarilumab joins tocilizumab as a second SC IL-6 inhibitor treatment option. Two additional JAK inhibitors, baricitinib and upadacitinib, provide more oral options for patients unable to tolerate MTX or TNFis.

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