MEDICATION COVERAGE POLICY

PHARMACY AND THERAPEUTICS ADVISORY COMMITTEE

POLICY:	Rheumatoid Arthritis (RA)	**P&T DATE:**	6/10/2025
CLASS:	Rheumatology/Anti-inflammatory Disorders	**REVIEW HISTORY** (*month/year*)	6/24, 6/23, 9/21, 09/20, 05/19, 02/18, 02/17, 2/16, 5/15, 10/14, 2/13, 2/12, 5/10, 2/08, 2/07, 11/22
LOB:	Medi-Cal		

This policy has been developed through review of medical literature, consideration of medical necessity, generally accepted medical practice standards, and approved by the Health Plan of San Joaquin/Mountain Valley Health Plan (Health Plan) Pharmacy and Therapeutic Advisory Committee.

Effective 1/1/2022, the Pharmacy Benefit is regulated by Medi-Cal Rx. Please visit https://medi-calrx.dhcs.ca.gov/home/ for portal access, formulary details, pharmacy network information, and updates to the pharmacy benefit.

All medical claims require that an NDC is also submitted with the claim. If a physician administered medication has a specific assigned CPT code, that code must be billed with the correlating NDC. If there is not a specific CPT code available for a physician administered medication, the use of unclassified CPT codes is appropriate when billed with the correlating NDC.

Any biosimilars pending litigations or not officially available in the US Market for consumer use is not an available treatment option or covered on the medical benefit. Biosimilars that are FDA approved and available in the US Market for consumer use will follow the reference brand name criteria as available per our PH05 - Prior Authorizations processes. Certain biosimilars may be subject to alternative criteria based on the preferences of Health Plan.

OVERVIEW

Rheumatoid Arthritis (RA) is an inflammatory condition that usually involves small joints and estimated to affect 1.3 million individuals in the U.S. with 75% of patients suffering from RA being female.[1] Early manifestations of RA include joint pain, stiffness, and swelling. Progression of RA will lead to permanent joint damage and deformity. This review will examine the treatment guidelines of RA, the currently available RA drug products, and their coverage criteria.

Available Rheumatoid Arthritis Agents *(Current as of 01/2025)*

CPT Code	Generic Name (Brand Name)	Available Strengths	Pharmacy Benefit	Outpatient Medical Benefit (restrictions)
Oral DMARDs				
--	**Azathioprine** (Imuran)	Tablets: 50mg, 75mg, 100mg	Yes	No
--	**Cyclosporine**, micronized	Capsules: 25mg, 100mg	Yes	No
--	**Leflunomide** (Arava)	Tablets: 10mg	Yes	No
J9260 for vials	**Methotrexate** (Trexall)	Tablets: 2.5mg Auto-injector: 10 mg/0.4mL, 7.5 mg/0.15 mL, and others Solution: 25mg/2ml	Yes	No
--	**Sulfasalazine** (Azulfidine)	Tablet, DR Tablet: 500mg	Yes	No
Tumor Necrosis Factor Inhibitor				
J0135	**Adalimumab** (Humira)	Pen-injector Kit,	Yes	No

		Prefilled Syringe kit: 20mg/0.4ml, 40mg/0.8ml		
Q5131 (Idacio) Q5132 (Abrilada)	Adalimumab biosimilars **Adalimumab-adbm** (Cyltezo), **Adalimumab-atto** (Amjevita) **Adalimumab-afzb** (Abrilada) **Adalimumab-bwwd** (Hadlima) **Adalimumab-aacf** [Idacio]		Yes	No
J1438	**Etanercept** (Enbrel)	Auto-injector, cartridge, prefilled syringe: 25mg/ml, 50mg/ml Solution: 25 mg/0.5 mL	Yes	No
--	**Etanercept-szzs** (Erelzi)			
Q5103	**Infliximab-dyyb** (Inflectra)	Solution: 100mg	Yes	Yes (PA)
Q5104	**Infliximab-abda** (Renflexis)	Solution: 100mg	Yes	Yes (PA)
Q5121	**Infliximab-axxq** (Avsola)	Solution: 100mg	Yes	Yes (PA)
Q5109	**Infliximab-qbtx** (Ixifi)	Solution: 100mg	Yes	Yes (PA)
J1745	**Infliximab** (Remicade)	Solution: 100mg	Yes	Yes (PA)
J1602 for IV solution	**Golimumab** (Simponi, Simponi Aria)	Auto-injector, prefilled syringe: 50mg/0.5ml, 100mg/ml Solution: 50mg/4ml	Yes, for auto-injector and prefilled syringe	Yes, for solution for IV administration (PA)
J0717	**Certolizumab** (Cimzia)	Vials, auto-injector, prefilled syringes: 200mg/ml	Yes, for prefilled syringes and auto-injectors	Yes, for vials (PA)
Other Therapies				
Interleukin-6 Receptor Antagonist				
--	**Sarilumab** (Kevzara)	Prefilled syringe, auto-injector: 150mg/1.14ml, 200mg/1.14ml	Yes	No
J3262	**Tocilizumab** (Actemra)	Auto-injector, prefilled syringe: 162mg/0.9ml; Solution: 80mg/4ml IV vial, 200mg/10ml IV vial, 400mg/20ml IV vial	Yes	Yes, for solution for IV administration (PA)
Q5133	**Tocilizumab-bavi (Tofidence)**	IV Solution: Tocilizumab-bavi 80 mg/4 mL (4 mL); Tocilizumab-bavi 400 mg/20 mL (20 mL); Tocilizumab-bavi 200 mg/10 mL (10 mL)	Yes	Yes, for solution for IV administration (PA)
Q5135	**Tocilizumab-aazg (Tyenne)**	IV Solution: Tocilizumab-aazg 200 mg/10 mL (10 mL); Tocilizumab-aazg 400 mg/20 mL (20 mL) SQ Auto-injector, Prefilled Syringe: Tocilizumab-aazg 162 mg/0.9 mL (0.9 mL)	Yes	Yes, for solution for IV administration (PA)
Selective T-Cell Costimulation Blocker				
J0129	**Abatacept** (Orencia)	Auto-injector: 125 mg/mL Prefilled syringe: 50 mg/0.4 mL, 87.5 mg/0.7mL, 125mg/ml Solution: 250mg	Yes, for prefilled syringe and auto-injector	Yes, for reconstituted solution (PA)

Anti-CD20 Monoclonal Antibody				
J9312 (replaces J9310)	**Rituximab** (Rituxan)	Solution: 10mg/ml vial	Yes	Yes (PA)
Q5115	**Rituximab-abbs** (Truxima)	Solution: 10mg/ml vial	Yes	Yes (PA)
Q5119	**Rituximab-pvvr** (Ruxience)	Solution: 10mg/ml vial	Yes	Yes (PA)
Q5123	**Rituximab-arrx** (Riabni)	Solution: 10mg/ml vial	Yes	Yes (PA)
Janus Kinase Inhibitor				
--	**Baricitinib** (Olumiant)	Tablets: 2mg	Yes	No
--	**Tofacitinib** (Xeljanz)	Tablets: 5mg, 11mg Tablets, XR: 11 mg, 22 mg Oral solution: 1mg/mL	Yes	No
--	**Upadacitinib** (Rinvoq)	Tablets: 15mg, 30 mg, 45 mg	Yes	No
Interleukin-1 Receptor Antagonist				
--	**Anakinra** (Kineret)	Prefilled syringe: 100mg/0.67ml	Yes	No

EVALUATION CRITERIA FOR APPROVAL/EXCEPTION CONSIDERATION

Below are the coverage criteria and required information for each agent. These coverage criteria have been reviewed approved by the HPSJ/MVHP Pharmacy & Therapeutics (P&T) Advisory Committee. For conditions not covered under this Coverage Policy, HPSJ/MVHP will make the determination based on Medical Necessity as described in HPSJ/MVHP Medical Review Guidelines (UM06).

Biologics

1st line— Infliximab (Remicade, Renflexis, Inflectra, Avsola), Rituximab biosimilar (Riabni, Ruxience, Truxima), Golimumab (Simponi)

- ❒ **Coverage Criteria:** Reserved for treatment failure to either
  - **(a)** 12 weeks of dose-optimized, oral DMARD therapy (Methotrexate 15-25mg/week, Leflunomide, Hydroxychloroquine, Sulfasalazine, Azathioprine). (If patient is unable to tolerate one oral DMARD, a second oral DMARD must be tried) OR
  - **(b)** a previous biologic or its biosimilars (e.g. Adalimumab, Sarilumab, Anakinra) OR
  - **(c)** a previous JAK inhibitor (Baricitinib, Tofacitinib, Upadacitinib)
- ❒ **Limits:** None
- ❒ **Required Information for Approval:** Prescription history showing at least 3 month trial of one oral DMARD and/or history of biologic or JAK inhibitor therapy.
- ❒ **Other Notes:** Must be initiated by a rheumatologist.

2nd line—Certolizumab (Cimzia), Tocilizumab (Actemra, Tyenne, Tofidence), Abatacept (Orencia), Rituximab (Rituxan)

- ❒ **Coverage Criteria:**
  - **Tocilizumab** and **Rituximab (Rituxan)** are reserved for treatment of rheumatoid arthritis with treatment failure to **Adalimumab**, **Etanercept**, **Infliximab**, **Golimumab, Sarilumab, or Rituximab biosimilars**. Must be prescribed by a rheumatologist.
  - **Certolizumab** is reserved for treatment of rheumatoid arthritis and must meet one of the following:

        - [1] treatment failure/documented intolerance to **Adalimumab**, **Etanercept**, **Infliximab**, **Golimumab, Sarilumab, or Rituximab** OR
        - [2] women that are currently pregnant or breastfeeding. Must be prescribed by a rheumatologist or dermatologist.
    - **Abatacept** is reserved for treatment of rheumatoid arthritis and must meet one of the following:
        - [1] treatment failure/documented intolerance to **Adalimumab**, **Etanercept**, **Infliximab**, **Golimumab, Sarilumab, or Rituximab** OR
        - [2] patients with
            - (a) nontuberculous mycobacterial lung disease OR contraindications to TNFi biologics, including congestive heart failure, previous serious infections, recurrent infections, or demyelinating disease AND
            - (b) who have treatment failure to 12 weeks of dose-optimized, oral DMARD therapy (Methotrexate 15-25mg/week, Leflunomide, Hydroxychloroquine, Sulfasalazine, Azathioprine).

- ❒ **Limits:** None
- ❒ **Required Information for Approval:** One of the following: [1] prescription history showing at least 3 month trial of one first line agent (Infliximab, Rituximab biosimilar, or Golimumab) OR [2] clinic notes documenting a current pregnancy or nursing of a breastfed child (for Cimzia).
- ❒ **Other Notes:** Must be initiated by a rheumatologist.

⌖ CLINICAL JUSTIFICATION

The European League against Rheumatism (EULAR)

The European League against Rheumatism (EULAR) made the following recommendations for rheumatoid arthritis management for the EULAR 2019 Update[31]:

1. Therapy with DMARDs should be started as soon as the diagnosis of RA is made.
2. Treatment should be aimed at reaching a target of sustained remission or low disease activity in every patient.
3. Monitoring should be frequent in active disease (every 1-3 months); if there is no improvement by at most 3 months after the start of treatment or the target has not been reached by 6 months, therapy should be adjusted.
4. MTX should be part of the first treatment strategy.
5. In patients with a contraindication to MTX (or early intolerance), leflunomide or sulfasalazine should be considered as part of the (first) treatment strategy
6. Short-term glucocorticoids should be considered when initiating or changing csDMARDs, in different dose regimens and routes of administration, but should be tapered as rapidly as clinically feasible.
7. If the treatment target is not achieved with the first csDMARD strategy, in the absence of poor prognostic factors, other csDMARDs should be considered.
8. If the treatment target is not achieved with the first csDMARD strategy, when poor prognostic factors are present, a bDMARD or tsDMARD should be added.
9. bDMARDs and tsDMARDs should be combined with a csDMARD; in patients who cannot use csDMARDs as comedication, IL-6 pathway inhibitors and tsDMARDs may have some advantages compared with other bDMARDs.
10. If a bDMARD or tsDMARD has failed, treatment with another bDMARD or a tsDMARD should be considered; if one TNF inhibitor therapy has failed, patients may receive an agent with another mode of action or a second TNF inhibitor.

11. If a patient is in persistent remission after having tapered glucocorticoids, one can consider tapering bDMARDs or tsDMARDs, especially if this treatment is combined with a csDMARD.
12. If a patient is in persistent remission, tapering the csDMARD could be considered.

DMARDs: biological DMARDs; DMARDs: conventional synthetic DMARDs (methotrexate, leflunomide, sulfasalazine, hydroxychloroquine); DMARDs: disease-modifying antirheumatic drugs; MTX, methotrexate; RA, rheumatoid arthritis; RCT, randomized controlled trial; TNF, tumor necrosis factor; tsDMARDs, targeted synthetic DMARDs (tofacitinib, baricitinib, upadacitinib).

The American College of Rheumatology

The American College of Rheumatology (ACR) 2015 Guidelines[2] and the 2021 Guidelines[42] for Treatment of Rheumatoid Arthritis recommend the following:

Treat-to-Target Approach

The 2015 ACR guidelines strongly emphasize the "treat to target" approach—that is, adjust a patient's therapeutic regimen as necessary to achieve a specific goal rather than treating without a measureable goal. Treatment goal is usually to achieve remission or low disease activity. The ACR approves 6 different assessment tools *(see Figure 1 below)* that objectively calculates patient's disease activity. Evidence suggests patients on RA therapies benefit the most when providers practice the "treat to target" approach.

Figure 1: ACR recommended Instruments to measure RA disease activity

Instrument (reference)	Thresholds of disease activity
Patient Activity Scale (PAS) or PASII (range 0–10) (149)	Remission: 0–0.25 Low activity: >0.25–3.7 Moderate activity: >3.7 to <8.0 High activity: ≥8.0
Routine Assessment of Patient Index Data 3 (RAPID3) (range 0–10) (155)	Remission: 0–1.0 Low activity: >1.0–2.0 Moderate activity: >2.0–4.0 High activity: >4.0–10
Clinical Disease Activity Index (CDAI) (range 0–76.0) (156)	Remission: ≤2.8 Low activity: >2.8–10.0 Moderate activity: >10.0–22.0 High activity: >22
Disease Activity Score (DAS) 28 erythrocyte sedimentation rate (ESR) (range 0–9.4) (157)	Remission: <2.6 Low activity: ≥2.6 to <3.2 Moderate activity: ≥3.2 to ≤5.1 High activity: >5.1
Simplified Disease Activity Index (SDAI) (range 0–86.0) (158)	Remission: ≤3.3 Low activity: >3.3 to ≤11.0 Moderate activity: >11.0 to ≤26 High activity: >26

* These 6 measures were endorsed by the American College of Rheumatology in 2012 (16). Other measures are now available to clinicians, but they were not included in this guideline because it was beyond the scope of this review. Adapted from ref. 16.

Early RA Patients

Low Disease Activity (DMARD-naïve)

- Hydroxychloroquine is conditionally recommended over other conventional synthetic (csDMARDs).
- Sulfasalazine is conditionally recommended over methotrexate.
- Methotrexate is conditionally recommended over leflunomide.

Moderate-High Disease Activity (DMARD-naïve)

- Methotrexate is strongly recommended over hydroxychloroquine or sulfasalazine.
- Methotrexate is conditionally recommended over leflunomide.
- Methotrexate monotherapy is strongly recommended over bDMARD or tsDMARD monotherapy.
- Methotrexate monotherapy is conditionally recommended over dual or triple csDMARD therapy.
- Methotrexate monotherapy is conditionally recommended over methotrexate plus a tumor necrosis factor (TNF) inhibitor.
- Methotrexate monotherapy is strongly recommended over methotrexate plus a non–TNF inhibitor bDMARD or tsDMARD.
- Corticosteroid use
    - Initiation of a csDMARD *without* short-term (<3 months) glucocorticoids is conditionally recommended over initiation of a csDMARD with short-term glucocorticoids.

- Initiation of a csDMARD *without* longer-term (≥3 months) glucocorticoids is strongly recommended over initiation of a csDMARD with longer-term glucocorticoids for DMARD-naive patients with moderate-to-high disease activity.

Recommendations for treatment modification in patients treated with DMARDs who are not at target

- Treatment approach
  - A treat-to-target approach is strongly recommended over usual care for patients who have not been previously treated with bDMARDs or tsDMARDs
  - A treat-to-target approach is conditionally recommended over usual care for patients who have had an inadequate response to bDMARDs or tsDMARDs
  - A minimal initial treatment goal of low disease activity is conditionally recommended over a goal of remission
- Modification of DMARD(s)
  - Addition of a bDMARD or tsDMARD is conditionally recommended over triple therapy (i.e., addition of sulfasalazine and hydroxychloroquine) for patients taking maximally tolerated doses of methotrexate who are not at target
  - Switching to a bDMARD or tsDMARD of a different class is conditionally recommended over switching to a bDMARD or tsDMARD belonging to the same class for patients taking a bDMARD or tsDMARD who are not at target
- Use of glucocorticoids
  - Addition of/switching to DMARDs is conditionally recommended over continuation of glucocorticoids for patients taking glucocorticoids to remain at target
  - Addition of/switching to DMARDs (with or without intraarticular [IA] glucocorticoids) is conditionally recommended over the use of IA glucocorticoids alone for patients taking DMARDs who are not at target
- Recommendations for tapering/discontinuing DMARDs
  - Continuation of all DMARDs at their current dose is conditionally recommended over a dose reduction of a DMARD, dose reduction is conditionally recommended over gradual discontinuation of a DMARD, and gradual discontinuation is conditionally recommended over abrupt discontinuation of a DMARD for patients who are at target for at least 6 months
  - Gradual discontinuation of sulfasalazine is conditionally recommended over gradual discontinuation of hydroxychloroquine for patients taking triple therapy who wish to discontinue a DMARD
  - Gradual discontinuation of methotrexate is conditionally recommended over gradual discontinuation of the bDMARD or tsDMARD for patients taking methotrexate plus a bDMARD or tsDMARD who wish to discontinue a DMARD

In addition, the guidelines provide recommendations for specific patient populations.

- Subcutaneous nodules
  - Methotrexate is conditionally recommended over alternative DMARDs for patients with subcutaneous nodules who have moderate-to-high disease activity
  - Switching to a non-methotrexate DMARD is conditionally recommended over continuation of methotrexate for patients taking methotrexate with progressive subcutaneous nodules
- Pulmonary disease
  - Methotrexate is conditionally recommended over alternative DMARDs for the treatment of inflammatory arthritis for patients with clinically diagnosed mild and stable airway or parenchymal lung disease who have moderate-to-high disease activity.
- Heart failure
  - Addition of a non–TNF inhibitor bDMARD or tsDMARD is conditionally recommended over addition of a TNF inhibitor for patients with NYHA class III or IV heart failure and an inadequate response to csDMARDs.
  - Switching to a non–TNF inhibitor bDMARD or tsDMARD is conditionally recommended over continuation of a TNF inhibitor for patients taking a TNF inhibitor who develop heart failure.

- Lymphoproliferative disorder
    - Rituximab is conditionally recommended over other DMARDs for patients who have a previous lymphoproliferative disorder for which rituximab is an approved treatment and who have moderate-to-high disease activity
- Hepatitis B infection
    - Prophylactic antiviral therapy is strongly recommended over frequent monitoring alone for patients initiating rituximab who are hepatitis B core antibody positive (regardless of hepatitis B surface antigen status).
    - Prophylactic antiviral therapy is strongly recommended over frequent monitoring alone for patients initiating any bDMARD or tsDMARD who are hepatitis B core antibody positive and hepatitis B surface antigen positive.
    - Frequent monitoring alone is conditionally recommended over prophylactic antiviral therapy for patients initiating a bDMARD other than rituximab or a tsDMARD who are hepatitis B core antibody positive and hepatitis B surface antigen negative.
- Nonalcoholic fatty liver disease
    - Methotrexate is conditionally recommended over alternative DMARDs for DMARD-naive patients with nonalcoholic fatty liver disease, normal liver enzymes and liver function tests, and no evidence of advanced liver fibrosis who have moderate-to high disease activity.
- Persistent hypogammaglobulinemia without infection
    - In the setting of persistent hypogammaglobulinemia without infection, continuation of rituximab therapy for patients at target is conditionally recommended over switching to a different bDMARD or tsDMARD.
- Previous serious infection
    - Addition of csDMARDs is conditionally recommended over addition of a bDMARD or tsDMARD for patients with a serious infection within the previous 12 months who have moderate-to-high disease activity despite csDMARD monotherapy
    - Addition of/switching to DMARDs is conditionally recommended over initiation/ dose escalation of glucocorticoids for patients with a serious infection within the previous 12 months who have moderate-to-high disease activity.
- Nontuberculous mycobacterial lung disease
    - Use of the lowest possible dose of glucocorticoids (discontinuation if possible) is conditionally recommended over continuation of glucocorticoids for patients with nontuberculous mycobacterial lung disease.
    - Addition of csDMARDs is conditionally recommended over addition of a bDMARD or tsDMARD for patients with nontuberculous mycobacterial lung disease who have moderate-to-high disease activity despite csDMARD monotherapy.
    - Abatacept is conditionally recommended over other bDMARDs and tsDMARDs for patients with nontuberculous mycobacterial lung disease who have moderate-to-high disease activity despite csDMARDs.

Per the package insert, certolizumab pegol concentrations were minimal/undetectable in multiple samples of infant plasma and in breast milk.[40] Multiple disease-modifying anti-rheumatic drugs (DMARDs) are to be avoided during pregnancy and lactation (see Figures 1 and 2).[32,33,37,41] Hence, patients that are pregnant or currently breastfeeding and have a clinical indication for Cimzia treatment can bypass usual step therapy requirements for Cimzia treatment.[32-41]

Figure 1. 2016 EULAR recommendations for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation.[32]

Overarching principles

A	Family planning should be addressed in each patient of reproductive age and adjustment of therapy considered before a planned pregnancy.
B	Treatment of patients with rheumatic disease before/during pregnancy and lactation should aim to prevent or suppress disease activity in the mother and expose the fetus/child to no harm.
C	The risk of drug therapy for the child should be weighed against the risk that untreated maternal disease represents for the patient and the fetus or child.
D	The decision on drug therapy during pregnancy and lactation should be based on agreement between the internist/rheumatologist, gynaecologist/obstetrician and the patient, and including other healthcare providers when appropriate.

*Points to consider for use of antirheumatic drugs in pregnancy**		Grade of recommendation†
1	csDMARDs‡ proven compatible with pregnancy are hydroxychloroquine, chloroquine, sulfasalazine, azathioprine, ciclosporin, tacrolimus and colchicine. They should be continued in pregnancy for maintenance of remission or treatment of a disease flare.	B
2	csDMARDs‡ methotrexate, mycophenolate mofetil and cyclophosphamide are teratogenic and should be withdrawn before pregnancy.	B
3	Non-selective COX inhibitors (non-steroidal anti-inflammatory drugs, NSAIDs) and prednisone should be considered for use in pregnancy if needed to control active disease symptoms. NSAIDs should be restricted to the first and second trimesters.	B
4	In severe, refractory maternal disease during pregnancy methylprednisolone pulses, intravenous immunoglobulin or even second or third trimester use of cyclophosphamide should be considered.	D
5	csDMARDs‡, tsDMARDs§ and anti-inflammatory drugs with insufficient documentation concerning use in pregnancy should be avoided until further evidence is available. This applies to leflunomide, mepacrine, tofacitinib and selective COX II inhibitors.	B–D
6	Among bDMARDs¶ continuation of tumour necrosis factor (TNF) inhibitors during the first part of pregnancy should be considered. Etanercept and certolizumab may be considered for use throughout pregnancy due to low rate of transplacental passage.	B
7	bDMARDs¶ rituximab, anakinra, tocilizumab, abatacept, belimumab and ustekinumab have limited documentation on safe use in pregnancy and should be replaced before conception by other medication. They should be used during pregnancy only when no other pregnancy-compatible drug can effectively control maternal disease.	D

*Points to consider for use of antirheumatic drugs during lactation**		Grade of recommendation†
1	csDMARDs‡ and anti-inflammatory drugs compatible with breast feeding should be considered for continuation during lactation provided the child does not have conditions that contraindicate it. This applies to hydoxychloroquine, chloroquine, sulfasalazine, azathioprine, ciclosporin, tacrolimus, colchicine, prednisone, immunoglobulin, non-selective COX inhibitors and celecoxib.	D
2	csDMARDs‡, tsDMARDs§ and anti-inflammatory drugs with no or limited data on breast feeding should be avoided in lactating women. This applies to methotrexate, mycophenolate mofetil, cyclophosphamide, leflunomide, tofacitinib and *cyclooxygenase* II inhibitors other than celecoxib.	D
3	Low transfer to breast milk has been shown for infliximab, adalimumab, etanercept and certolizumab. Continuation of TNF inhibitors should be considered compatible with breast feeding.	D
4	bDMARDs¶ with no data on breast feeding such as rituximab, anakinra, belimumab, ustekinumab, tocilizumab and abatacept should be avoided during lactation if other therapy is available to control the disease. Based on pharmacological properties of bDMARDs¶, lactation should not be discouraged when using these agents, if no other options are available.	D

*Level of evidence is given for each drug separately in table 2.
†**A** Category I evidence from meta-analysis of randomised controlled trials (1A) or from at least one randomised controlled trial (1B)
B Category II evidence from at least one controlled study without randomisation (2A) or from at least one type of quasi-experimental study (2B), or extrapolated recommendations from category I evidence.
C Category III evidence from descriptive studies, such as comparative studies, correlation studies or case-control studies (3), or extrapolated recommendation from category I or II evidence.
D Category IV evidence from expert committee reports or opinions and/or clinical experience of respected authorities (4), or extrapolated recommendation from category II or III evidence.[10]
‡Conventional synthetic DMARDs.
§Targeted synthetic DMARDs.
¶Biologic DMARDs.

Figure 2. Recommendations by the American College of Rheumatology Guideline for the Management of Reproductive Health in Rheumatic and Musculoskeletal Diseases.[33]

Medication	Pre-conception	During pregnancy	Breastfeeding
Conventional medications			
Hydroxychloroquine	++	++	++
Sulfasalazine	++	++	++
Colchicine	++	++	++
Azathioprine, 6-mercaptopurine	++	++	+ Low transfer
Prednisone	+ Taper to <20 mg/day by adding pregnancy-compatible immunosuppressants	+ Taper to <20 mg/day by adding pregnancy-compatible immunosuppressants	+ After a dose of >20 mg, delay breastfeeding for 4 hours
Cyclosporine, tacrolimus	+ Monitor blood pressure	+ Monitor blood pressure	+ Low transfer
Nonsteroidal antiinflammatory drugs (cyclooxygenase 2 inhibitors not preferred)	+ Discontinue if the woman is having difficulty conceiving	+ Continue in first and second trimesters; discontinue in third trimester	+ Ibuprofen preferred
Tumor necrosis factor inhibitors (tumor necrosis factor inhibitors are considered compatible with pregnancy)			
Certolizumab	++	++	++
Infliximab, etanercept, adalimumab, golimumab	+ Continue through conception	+ Continue in first and second trimesters; discontinue in third trimester several half-lives prior to delivery	++
Rituximab	+ Discontinue at conception	+ Life-/organ-threatening disease	++
Other biologics (limited safety data; limited transfer in early pregnancy but high transfer in second half of pregnancy)			
Anakinra, belimumab, abatacept, tocilizumab, secukinumab, ustekinumab	+ Discontinue at conception	× Discontinue during pregnancy	+ Expect minimal transfer due to large molecular size, but no available data
Not compatible with pregnancy			
Methotrexate	×× Stop 1–3 months prior to conception	×× Stop and give folic acid 5 mg/day	× Limited data suggest low transfer
Leflunomide	×× Cholestyramine washout if detectable levels	×× Stop and give cholestyramine washout	××
Mycophenolate mofetil and mycophenolic acid	×× Stop >6 weeks prior to conception to assess disease stability	××	××
Cyclophosphamide	×× Stop 3 months prior to conception	+ Life-/organ-threatening disease in second and third trimesters	××
Thalidomide	×× Stop 1–3 months prior to conception	××	××
Tofacitinib, apremilast, baricitinib	Unable to determine due to lack of data; small molecular size suggests transfer across the placenta and into breast milk		

++ Strongly recommend

\+ Conditionally recommend

× Conditionally recommend against

×× Strongly recommend against

The 2015 ACR Guidelines and 2016 EULAR guidelines recommend initiating 3-month DMARD monotherapy (Methotrexate or Leflunomide) for patients with low disease activity without poor prognosis. Poor prognosis is defined as: presence of 1 or more of the following features: functional limitation (e.g., HAQ DI or similar valid tools), extraarticular disease (e.g., presence of rheumatoid nodules, RA vasculitis, Felty's syndrome), positive rheumatoid factor, or bony erosions by radiograph. For patients not responding to monotherapy, the guidelines recommend adding another or switching to a non-methotrexate DMARD. Patients still not responding may need to add or switch to a TNF inhibitor.

For patients with moderate/severe disease activity or patients with low disease activity but poor prognosis, initiate 3-month trial of Methotrexate or consider combinational (dual or triple) DMARD therapy. Unresponsive patients may require adding a biologic therapy. Most biologics require 3 months to observe therapeutic benefits. However, certain biologics (Abatacept, Rituximab, Ustekinumab), require 6 months or longer before the full benefits are seen. The efficacy between biologics do not differ significantly but the cost may vary due to differences in administration frequency (twice monthly vs. weekly vs. monthly, and so forth). Therefore, HPSJ/MVHP's order of preference of the biologic therapies are based on the cost-benefit ratio where the first-line biologics are agents associated with the lowest cost-benefit ratio.

Xeljanz had similar efficacy rates to Humira in the ORAL Standard trial where Humira was an active control group, but no formal non-inferiority analysis was performed.[3] Further head-on trials are needed in order to determine the role of Xeljanz. For this reason, the 2015 ACR guidelines recommend Xeljanz as last line therapy if patients have an insufficient response to TNF inhibitors.

Role of oral agents (DMARDs and immunosuppressants)

Oral DMARDs are commonly used as first-line therapies in many mild-moderate inflammatory disorders with a few exceptions (e.g. Ankylosing Spondylitis). For most patients, treatment with oral agents may be sufficient for their condition. Generally, 12 weeks of continuous DMARD therapy is considered to be an adequate trial—assuming the drug is adequately dosed. In patients with liver and/or renal impairment, DMARDs are not necessarily excluded right away. In most cases, DMARDs can be safely used as long as there is regular monitoring of labs and side effects and the dosing is adjusted accordingly.

Table 1: Commonly used oral agents in chronic inflammatory diseases

Oral Agent	Joint	Skin	GI	liver damage	kidney damage	Pregnancy	Breastfeeding
Azathioprine	X	X*	X	monitor	monitor & dose adjust	Avoid use	Not recommended
Cyclosporine	X*	X	X*	monitor	monitor & dose adjust	Avoid use	Not recommended
Hydroxychloroquine	X		X*	monitor	monitor	Generally safe	Generally safe
Leflunomide	X	X	X*	avoid use	avoid use	Contraindicated	Unknown
Mercaptopurine	X*	X*	X	monitor	monitor & dose adjust	Avoid use	Unknown
Methotrexate	X	X	X	avoid use	monitor & dose adjust	Contraindicated	Contraindicated
Sulfasalazine	X	X*	X	monitor	monitor	Generally safe	Generally safe

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⌖ REVIEW & EDIT HISTORY

Document Changes	Reference	Date	P&T Chairman
Creation of Policy	Psoriasis - biologicals 2-20-07.doc	2/2007	Allen Shek, PharmD
Updated Policy	Biological Response Modifiers Review 2-19-08.doc	2/2008	Allen Shek, PharmD
Updated Policy	Biologic Response Modifiers 2010 final.docx	5/2010	Allen Shek, PharmD
Updated Policy	TNF MUE summary 2-21-2012.docx	2/2012	Allen Shek, PharmD
Updated Policy	Xeljanz Monograph 2013-02-13.docx	2/2013	Allen Shek, PharmD
Updated Policy	Psoriatic Arthritis & Ankylosing Spondylitis.docx	10/2014	Jonathan Szkotak, PharmD
Updated Policy	HPSJ Coverage Policy - Rheum & Immuno - Rheumatoid Arthritis 2015-05.docx	9/2015	Jonathan Szkotak, PharmD
Updated Policy	Class Review- Biologics, Apremilast, and Tofacitinib in Inflammatory Joint, Skin, and Bowel Diseases.docx	2/2016	Johnathan Yeh, PharmD
Updated Policy	Class Review- Biologics, Apremilast, and Tofacitinib in Inflammatory Joint, Skin, and Bowel Diseases.docx	02/2017	Johnathan Yeh, PharmD
Updated Policy	HPSJ Coverage Policy - Rheum & Immuno - Rheumatoid Arthritis 2018-02.docx	02/2018	Johnathan Yeh, PharmD
Updated Policy	HPSJ Coverage Policy - Rheum & Immuno - Rheumatoid Arthritis 2019-05.docx	05/2019	Matthew Garrett, PharmD
Updated Policy	HPSJ Coverage Policy - Rheum & Immuno - Rheumatoid Arthritis 2020-09.docx	09/2020	Matthew Garrett, PharmD
Updated Policy	Rheumatoid Arthritis	09/2021	Matthew Garrett, PharmD
Updated Policy	Rheumatoid Arthritis	11/2022	Matthew Garrett, PharmD
Updated Policy	Rheumatoid Arthritis	6/2023	Matthew Garrett, PharmD
Update to Policy	Rheumatoid Arthritis	6/2024	Matthew Garrett, PharmD
Update to Policy	Rheumatoid Arthritis	6/2025	Matthew Garrett, PharmD

Note: All changes are approved by the Health Plan P&T Committee before incorporation into the utilization policy