Therapeutic Agents in Rheumatic and Inflammatory Diseases
Drug Class Prior Authorization Protocol

Line of Business: Medi-Cal
Effective Date: August 16, 2017
Revision Date: August 16, 2017

This policy has been developed through review of medical literature, consideration of medical necessity, generally accepted medical practice standards, and approved by the IEHP Pharmacy and Therapeutics Subcommittee.

**Drugs:** Actemra (tocilizumab), Cimzia (certolizumab), Cosentyx (secukinumab), Enbrel (etanercept), Entyvio (vedolizumab), Humira (adalimumab), Inflectra (infliximab-dyyb), Kevzara (sarilumab), Kineret (anakinra), Orencia (abatacept), Otezla (apremilast), Remicade (infliximab), Simponi, Simponi Aria (golimumab), Stelara (ustekinumab), Taltz (ixekizumab), Tysabri (natalizumab), Xeljanz (tofacitinib)

**FDA Approved Indications:**

<table>
<thead>
<tr>
<th>Drug</th>
<th>AS</th>
<th>CD</th>
<th>UC</th>
<th>PP</th>
<th>PsA</th>
<th>RA</th>
<th>HS</th>
<th>MS</th>
<th>UV</th>
<th>pJIA</th>
<th>sJIA</th>
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<tbody>
<tr>
<td>Actemra (tocilizumab)</td>
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</table>

*AS = ankylosing spondylitis; CD = Crohn’s disease; UC = ulcerative colitis; pJIA = polyarticular juvenile idiopathic arthritis; sJIA = systemic juvenile idiopathic arthritis; PP = plaque psoriasis; PsA = psoriatic arthritis; RA = rheumatoid arthritis; HS = Hidradenitis Suppurativa; MS = multiple sclerosis; UV = uveitis*
Policy/Criteria:

A. **Drugs:** Actemra (tocilizumab), Cimzia (certolizumab), Enbrel (etanercept), Humira (adalimumab), Inflectra (infliximab-dyyb), Kevzara (sarilumab), Kineret (anakinra), Orencia (abatacept), Remicade (infliximab), Renflexis (infliximab-abda), Simponi, Simponi Aria (golimumab), Xeljanz (tofacitinib)

**Diagnosis:**
- a. Rheumatoid Arthritis

**Specialist:** Rheumatologist

**Criteria:**
- a. Trial and failure of at least one non-biologic DMARD (e.g. methotrexate, hydroxychloroquine, leflunomide, sulfasalazine, etc.)
- b. Failure or inadequate response to at least a 3-month treatment course of the two preferred biologic therapies: Enbrel and Humira, unless each were not tolerated or were contraindicated

**Authorization Duration:** 12 months

**Re-Authorization Criteria:**
- a. Documentation of meeting therapeutic goal (e.g. disease stability, improvement in daily activities and/or reduction in frequency of disease attacks)
- b. Requested dosage and administration are consistent with the FDA recommendations

**Formulary Status:**
- a. Enbrel and Humira: Non-formulary preferred; PA applies
- b. Others: Non-formulary, PA applies

B. **Drugs:** Cimzia (certolizumab), Cosentyx (secukinumab), Enbrel (etanercept), Humira (adalimumab), Inflectra (infliximab-dyyb), Remicade (infliximab), Renflexis (infliximab-abda), Simponi (golimumab)

**Diagnosis:**
- a. Ankylosing Spondylitis

**Specialist:** Rheumatologist

**Criteria:**
a. Failure or clinically significant adverse effects to at least one-month treatment course of one NSAID at maximal recommended dose or maximally tolerated dose
   AND
b. Failure or inadequate response to at least a 3-month treatment course of the two preferred biologic therapies: Enbrel and Humira, unless each were not tolerated or were contraindicated

Authorization Duration: 12 months

Re-Authorization Criteria:
   a. Documentation of meeting therapeutic goal (e.g. disease stability, improvement and/or reduction in frequency of disease attacks)
   AND
   b. Requested dosage and administration are consistent with the FDA recommendations

Formulary Status:
   a. Enbrel and Humira: Non-formulary preferred; PA applies
   b. Others: Non-formulary, PA applies

C. Drugs: Cimzia (certolizumab), Cosentyx (secukinumab), Enbrel (etanercept), Humira (adalimumab), Inflectra (infliximab-dyyb), Ocrevus (abatacept), Remicade (infliximab), Renflexis (infliximab-abda), Simponi (golimumab), Stelara (ustekinumab)

Diagnosis:
   a. Psoriatic arthritis

Specialist: Dermatologist, Rheumatologist

Criteria:
   a. Trial and failure of at least one non-biologic DMARD (e.g. methotrexate, leflunomide, sulfasalazine, etc.)
   AND
   b. Failure or inadequate response to at least a 3-month treatment course of the two preferred biologic therapies: Enbrel and Humira, unless each were not tolerated or were contraindicated

Authorization Duration: 12 months

Re-Authorization Criteria:
   a. Documentation of meeting therapeutic goal (e.g. disease stability, improvement and/or reduction in frequency of disease attacks)
   AND
b. Requested dosage and administration are consistent with the FDA recommendations

**Formulary Status:**

a. **Enbrel and Humira**: Non-formulary preferred; PA applies
b. **Others**: Non-formulary, PA applies

**D. Drugs:**

- **Cimzia** (certolizumab), **Entyvio** (vedolizumab), **Humira** (adalimumab), **Inflectra** (infliximab-dyyb), **Remicade** (infliximab), **Renflexis** (infliximab-abda), **Stelara** (ustekinumab, **Tysabri** (natalizumab)

**Diagnosis:**

a. Crohn’s Disease

**Specialist:** Gastroenterologist

**Criteria:**

a. Failure or clinically significant adverse effects to an adequate course of corticosteroids (e.g. oral budesonide 9mg/day, prednisone 40-60mg daily)
   OR
   Documentation that patient has been unable to taper corticosteroid therapy without experiencing worsening of disease
   AND
b. Treatment with at least a two-month course of DMARD (e.g. azathioprine, mercaptopurine or methotrexate) was not effective or not tolerated, unless all are contraindicated
   AND
   c. Failure or inadequate response to at least a 3-month treatment course of the preferred biologic therapies (see below), unless each were not tolerated or were contraindicated;
      i. **Humira**, then
      ii. **Cimzia**, then
      iii. **Renflexis** (pharmacy benefit, when supplied by pharmacy)
         OR
         **Renflexis** or **Inflectra** (medical benefit, e.g. J code)

**Authorization Duration:** 12 months

**Re-Authorization Criteria:**

a. Documentation of meeting therapeutic goal (e.g. disease stability, improvement and/or reduction in frequency of disease attacks)
   AND
b. Requested dosage and administration are consistent with the FDA recommendations
Formulary Status:
   a. **Humira**: Non-formulary preferred; PA applies  
   b. Others: Non-formulary, PA applies

E. **Drugs**: Cosentyx (secukinumab), Enbrel (etanercept), Humira (adalimumab), Inflectra (infliximab-dyyb), Remicade (infliximab), Renflexis (infliximab-abda), Stelara (ustekinumab), Taltz (ixeikizumab)

**Diagnosis:**
   a. Plaque psoriasis

**Specialist:** Dermatologist, Rheumatologist

**Criteria:**
   a. Documented psoriasis involvement of at least 10% of the body surface area  
      OR  
      Documented psoriasis involvement of the face, ears, hands, feet or genitalia  
      OR  
      Documented significant functional disability (i.e. unable to do daily activities)  
      AND  
   b. Trial and failure of at least one non-biologic DMARD (e.g. methotrexate, cyclosporine, azathioprine, etc.)  
      AND  
   c. Failure or inadequate response to at least a 3-month treatment course of the two preferred biologic therapies: **Enbrel** and **Humira**, unless each were not tolerated or were contraindicated

**Authorization Duration:** 12 months

**Re-Authorization Criteria:**
   a. Documentation of meeting therapeutic goal (e.g. disease stability, improvement and/or reduction in frequency of disease attacks)  
      AND  
   b. Requested dosage and administration are consistent with the FDA recommendations

**Formulary Status:**
   a. **Enbrel** and **Humira**: Non-formulary preferred; PA applies  
   b. Others: Non-formulary, PA applies
F. **Drugs:** Entyvio (vedolizumab), Humira (adalimumab), Inflectra (infliximab-dyyb), Remicade (infliximab), Renflexis (infliximab-abda), Simponi (golimumab)

**Diagnosis:**
- Ulcerative colitis

**Specialist:** Gastroenterologist

**Criteria:**
- Failure or clinically significant adverse effects to at least two of the conventional therapies:
  - An adequate course of corticosteroids (e.g. oral budesonide 9mg/day, prednisone 40-60mg daily or budesonide rectal)
  - At least one aminosalicylates (e.g. mesalamine, balsalazide, sulfasalazine)
  - Treatment with at least a two-month course of DMARD (e.g. azathioprine, mercaptopurine, methotrexate, sulfasalazine) was not effective or not tolerated, unless all are contraindicated

  **AND**

- Failure or inadequate response to at least a 2-month treatment course of the preferred biologic therapies (see below), unless each were not tolerated or were contraindicated.
  - Humira, then
  - Simponi, then
  - Renflexis (pharmacy benefit, when supplied by pharmacy)

  **OR**

  Renflexis or Inflectra (medical benefit, e.g. J code)

**Authorization Duration:** 12 months

**Re-Authorization Criteria:**
- Documentation of meeting therapeutic goal (e.g. disease stability, improvement and/or reduction in frequency of disease attacks)

  **AND**

- Requested dosage and administration are consistent with the FDA recommendations

**Formulary Status:**
- **Humira:** Non-formulary preferred; PA applies
- Others: Non-formulary, PA applies

G. **Drug:** Humira (adalimumab)

**Diagnosis:**
a. Non-Infectious Uveitis

**Specialist:** Ophthalmologist, Rheumatologist

**Criteria:**

a. Failure or clinically significant adverse effects to at least one oral corticosteroids (e.g. prednisone)
   
   AND
   
   b. Failure or clinically significant adverse effects to at least one non-biologic DMARD (e.g. azathioprine, cyclosporine, methotrexate, mycophenolate mofetil, tacrolimus, etc.)

**Authorization Duration:** 12 months

**Re-Authorization Criteria:**

a. Documentation of meeting therapeutic goal (e.g. disease stability, improvement and/or reduction in frequency of disease attacks)
   
   AND
   
   b. Requested dosage and administration are consistent with the FDA recommendations

**Formulary Status:** Non-formulary preferred, PA applies

**H. Drug: Ilaris (canakinumab)**

**Eligibility criteria:** Check CCS eligibility

**Diagnosis:**

a. Cryopyrin-Associated Periodic Syndromes (CAPS): Familial cold autoinflammatory syndrome or Muckle-Wells syndrome
   
   OR
   
   b. Familial Mediterranean fever (FMF)
   
   OR
   
   c. Tumor necrosis factor receptor-1 associated periodic syndrome (TRAPS) OR Hyperimmunoglobulin D Syndrome (HIDS)/Mevalonate Kinase Deficiency (MKD)
   
   OR
   
   d. Systemic Juvenile Idiopathic Arthritis

**Specialist:** Rheumatologist, Immunologist, specialist experienced in CAPS, FMF, TRAPS, HIDS or MKD

**Criteria:**
a. CAPS: Familial cold autoinflammatory syndrome or Muckle-Wells syndrome:
   i. Documented genetic confirmation of mutation in NLRP3;  
      **AND**
   ii. Documentation of significant functional impairment that limits daily living 
       activities;

b. Familial Mediterranean fever (FMF):
   i. Failure or clinically significant adverse effects to the alternative: colchicine

c. TRAPS, HIDS or MKD:
   i. Confirmed diagnosis by specialist

d. Systemic Juvenile Idiopathic Arthritis
   i. Failure or clinically significant adverse effects to: **Actemra AND Kineret**

**Authorization Duration:**
   a. Pending CCS eligibility: 1 month
   b. Not CCS eligible: 12 months

**Re-Authorization Criteria:**
   a. Documentation of meeting therapeutic goal (e.g. disease stability, improvement 
      and/or reduction in frequency of disease attacks) 
      **AND**
   b. Requested dosage and administration are consistent with the FDA 
      recommendations

**Formulary Status:** Non-formulary, PA applies

I. **Drug: Otezla** (apremilast)

**Diagnosis:**
   a. Plaque psoriasis
   **OR**
   b. Psoriatic arthritis

**Specialist:** Dermatologist, Rheumatologist

**Criteria:**
   a. Plaque psoriasis:
      i. Failure or clinically significant adverse effects to one of the preferred 
         biologic therapy: **Humira or Enbrel**
   b. Psoriatic arthritis:
      i. Failure or clinically significant adverse effects to one of the preferred 
         biologic therapy: **Humira or Enbrel**
Authorization Duration:
  a. 12 months

Re-Authorization Criteria:
  a. Documentation of meeting therapeutic goal (e.g. disease stability, improvement and/or reduction in frequency of disease attacks) AND
  b. Requested dosage and administration are consistent with the FDA recommendations

Formulary Status: Non-formulary, PA applies

Clinical Evidence:

2015 *American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis*

<table>
<thead>
<tr>
<th>Recommendations for patients with symptomatic Early RA</th>
<th>Level of Evidence (evidence reviewed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Regardless of disease activity level, use a treat-to-target strategy rather than a non-targeted approach (PICO A.1).</td>
<td>Low (17)</td>
</tr>
<tr>
<td>2. If the disease activity is low, in patients who have never taken a DMARD: • use DMARD monotherapy (MTX preferred) over double therapy (PICO A.2). • use DMARD monotherapy (MTX preferred) over triple therapy (PICO A.3).</td>
<td>Low (18-21) Low (22-25)</td>
</tr>
<tr>
<td>3. If the disease activity is moderate or high, in patients who have never taken a DMARD: • use DMARD monotherapy over double therapy (PICO A.4). • use DMARD monotherapy over triple therapy (PICO A.5).</td>
<td>Moderate (18,20,21) High (22-25)</td>
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<tr>
<td>4. If disease activity remains moderate or high despite DMARD monotherapy (with or without glucocorticoids), use combination DMARDS or a TNFi or a non-TNF biologic (all choices with or without MTX, in no particular order of preference), rather than continuing DMARD monotherapy alone (PICO A.7).</td>
<td>Low (26-28)</td>
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<tr>
<td>5. If disease activity remains moderate or high despite DMARDS: • use a TNFi monotherapy over tocitinib monotherapy (PICO A.8). • use a TNFi + MTX over tocitibin + MTX (PICO A.9).</td>
<td>Low (29) Low (30)</td>
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<tr>
<td>6. If disease activity remains moderate or high despite DMARD (PICO A.6) or biologic therapies (PICO A.12), add low-dose glucocorticoids.</td>
<td>Moderate (31-37) Low (31-37)</td>
</tr>
<tr>
<td>7. If disease flares, add short-term glucocorticoids at the lowest possible dose and for the shortest possible duration (PICO A.10, A.11).</td>
<td>Very low (38-43)</td>
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</tbody>
</table>

*Table 1: Recommendation for the treatment of patients with early RA:*
Figure 1: 2015 American College of Rheumatology recommendations update for the treatment of early rheumatoid arthritis (RA) defined as a disease duration < 6 months.
<table>
<thead>
<tr>
<th>Recommendations for patients with <strong>Established RA</strong></th>
<th>Level of Evidence (evidence reviewed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Regardless of disease activity level, use a treat-to-target strategy rather than a non-targeted approach (PICO B.1).</td>
<td>Moderate (44-46)</td>
</tr>
<tr>
<td>2. If the disease activity is low, in patients who have never taken a DMARD, use DMARD monotherapy (MTX preferred) over a TNFi (PICO B.2).</td>
<td>Low (47,48)</td>
</tr>
</tbody>
</table>
| 3. If the disease activity is moderate or high in patients who have never taken a DMARD:  
  - use DMARD monotherapy (MTX preferred) over tofacitinib (PICO B.3).  
  - use DMARD monotherapy (MTX preferred) over combination DMARD therapy (PICO B.4). | High (49)  
Moderate (18.20-25) |
| 4. If disease activity remains moderate or high despite DMARD monotherapy, use combination traditional DMARDs or add a TNFi or a non-TNF biologic or tofacitinib (all choices with or without MTX, in no particular order of preference), rather than continuing DMARD monotherapy alone (PICO B.5). | Moderate to Very low (23,26,29,30,47,48,50-59) |
| 5. If disease activity remains moderate or high despite TNFi therapy in patients who are currently not on DMARDs, add one or two DMARDs to TNFi therapy rather than continuing TNFi therapy alone (PICO B.6). | High (60-65) |
| 6. If disease activity remains moderate or high despite use of a single TNFi:  
  - use a non-TNF biologic, with or without MTX, over another TNFi with or without MTX (PICO B.12 and B.14).  
  - use a non-TNF biologic, with or without MTX, over tofacitinib with or without MTX (PICO B.13 and B.15). | Low to Very low (66-72)  
Very low<sup>a</sup> |
| 7. If disease activity remains moderate or high despite use of a single non-TNF biologic, use another non-TNF biologic, with or without MTX, over tofacitinib, with or without MTX (PICO B.16 and B.17). | Very low<sup>a</sup> |
| 8. If disease activity remains moderate or high despite use of multiple (2+) sequential TNFi therapies, first use a non-TNF biologic, with or without MTX, over another TNFi or tofacitinib (with or without MTX) (PICO B.8, B.9, B.10, B.11). | Very low (73-75) |
| 9. If the disease activity still remains moderate or high despite the use of multiple TNFi therapies, use tofacitinib, with or without MTX, over another TNFi, with or without MTX, if use of a non-TNF biologic is not an option (PICO B.23 and B.24). | Low (29,30) |
| 10. If disease activity remains moderate or high despite use of at least one TNFi and at least one non-TNF biologic:  
  - first use another non-TNF biologic, with or without MTX, over tofacitinib (PICO B.21 and B.22).  
  - if disease activity remains moderate or high, use tofacitinib, with or without MTX, over another TNFi (PICO B.19 and B.20). | Very low (29,30)  
Very low (29) |
| 11. If disease activity remains moderate or high despite use of DMARD, TNFi, or non-TNF biologic therapy, add short-term, low dose glucocorticoid therapy (PICO B.26 and B.27). | High to Moderate (33,41,76,77) |
| 12. If disease flares in patients on DMARD, TNFi, or non-TNF biologic therapy, add short-term glucocorticoids at the lowest possible dose and the shortest possible duration (PICO B.28 and B.29). | Very low (40-43) |
| 13. If the patient is in remission:  
  - taper DMARD therapy (PICO B.31)<sup>2</sup>.  
  - taper TNFi, non-TNF biologic, or tofacitinib (PICO B.33, B.35, B.37) (please also see #15). | Low<sup>3</sup> (78)  
Moderate to Very low<sup>3</sup> (79,80) |
| 14. If disease activity is low:  
  - continue DMARD therapy (PICO B.30).  
  - continue TNFi, non-TNF biologic or tofacitinib rather than discontinuing respective medication (PICO B.32, B.34 and B.36). | Moderate (78)  
High to Very low (79,80) |
| 15. If the patient’s disease is in remission, **do not** discontinue all RA therapies (PICO B.38). | Very low<sup>4</sup> |
Table 2: Recommendation for the treatment of patients with established RA

Figure 2: 2012 American College of Rheumatology (ACR) recommendations update for the treatment of established rheumatoid arthritis (RA) defined as a disease duration $\geq$ 6 months
### Table 3: Recommendation in RA patients with high-risk comorbidities

**2013 Update of the 2011 American College of Rheumatology Recommendations for the Treatment of Juvenile Idiopathic Arthritis (JIA)**

Systemic JIA with active systemic features and varying degrees of synovitis:

**Initial Therapeutic Options:**
- Anakinra (Kinereq) was recommended as one initial therapeutic option for patients with an physical global assessment (MD global) ≥5 irrespective of the active joint count (AJC), or a MD global <5 and an AJC >0 (level C).
- Systemic glucocorticoid (GC) monotherapy was recommended for a maximum period of 2 weeks as a therapeutic option for patients with an MD global <5 and an AJC >4 and for all patients with an MD global ≥5 irrespective of the AJC (Level C).
- Continuing GC as monotherapy for ≥1 month for patients with continued disease activity was inappropriate (Level D).

<table>
<thead>
<tr>
<th>High-risk condition</th>
<th>Recommendation</th>
<th>Level of Evidence (evidence reviewed)</th>
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<tbody>
<tr>
<td>Congestive heart failure</td>
<td>Use combination DMARDs or non-TNF biologic or tofacitinib over TNFi (PICO C.1, C.2 and C.3).</td>
<td>Moderate to Very low (83,84)</td>
</tr>
<tr>
<td>CHF worsening on current TNFi therapy</td>
<td>Use combination DMARDs or non-TNF biologic or tofacitinib over another TNFi (PICO C.4, C.5 and C.6).</td>
<td>Very low</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Use DMARDs over TNFi (PICO D.1).</td>
<td>Very low (85-92)</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>Use DMARDs over TNFi (PICO E.1).</td>
<td>Very low (92-103)</td>
</tr>
<tr>
<td>Hepatitis C infection and not receiving/requiring effective antiviral treatment</td>
<td>Use DMARDs over TNFi (PICO E.2).</td>
<td>Very low (92-103)</td>
</tr>
<tr>
<td>Past history of treated or untreated malignancy</td>
<td>Use DMARDs over biologics in melanoma (PICO F.1). Use DMARDs over tofacitinib in melanoma (PICO F.2). Use DMARDs over biologics in non-melanoma (PICO F.3). Use DMARDs over tofacitinib in non-melanoma (PICO F.4).</td>
<td>Very low (104-106)</td>
</tr>
<tr>
<td>Previously treated lymphoproliferative disorder</td>
<td>Use rituximab over TNFi (PICO G.1).</td>
<td>Very low (105,107)</td>
</tr>
<tr>
<td>Previously treated lymphoproliferative disorder</td>
<td>Use combination DMARD or abatacept or tocilizumab over TNFi (PICO G.2, G.3 and G.4).</td>
<td>Very low (105,107)</td>
</tr>
<tr>
<td>Previously treated solid organ malignancy</td>
<td>Same recommendations as in patients without this condition (PICO H.1).</td>
<td>Very low (105,108)</td>
</tr>
<tr>
<td>Previous Serious Infection(s)</td>
<td>Use combination DMARD over TNFi (PICO I.1). Use abatacept over TNFi (PICO I.2).</td>
<td>Very low (109-116)</td>
</tr>
</tbody>
</table>
• Initiating NSAID monotherapy in a patient without prior treatment was recommended as one approach for patients with an MD global <5 irrespective of the AJC (Level D). NSAID monotherapy was inappropriate for patients with an MD global ≥5 and an AJC >0 (Level D).

**Therapeutic Options for Continued Disease Activity**

• Use of abatacept (Orencia) was recommended only for patients with an MD global ≥5 and an AJC >4 after a trial of both an IL-1 inhibitor [e.g. anakinra (Kineret)] and tocilizumab (Actemra) sequentially (level D).
• Anakinra was recommended for patients with continued disease activity after treatment with GC monotherapy (level A) or NSAID monotherapy (level C).
• Use of a calcineurin inhibitor was recommended only for patients with an MD global ≥5 and an AJC of 0 after a trial of both an IL-1 inhibitor and tocilizumab sequentially (level C).
• Canakinumab (Ilaris) was recommended for patients with continued disease activity after treatment with GC monotherapy (level A), methotrexate or leflunomide (level A), anakinra (level B) or tocilizumab (level C).
• GC monotherapy was recommended as an option following failed treatment with NSAID monotherapy for patients with an MD global <5 and an AJC >0 and for patients with an MD global ≥5 irrespective of the AJC (level C). Adjunct GC therapy at any point was appropriate to consider (level D). Intraarticular GC injection was recommended as adjunct therapy at any time (level C).
• Methotrexate (MTX) or leflunomide was recommended for patients with an MD global <5 and an AJC >4 (level C).
• Initiation of a TNF inhibitor was recommended for patients with an AJC >4 irrespective of the MD global after a trial of an IL-1 inhibitor or tocilizumab (level C). Initiation of a TNF inhibitor was recommended for patients with an AJC >0 irrespective of the MD global after a trial of both an IL-1 inhibitor and tocilizumab sequentially (level C).

**Systemic JIA without active systemic features and with varying degrees of active synovitis:**

**Initial Therapeutic Options:**

• Intraarticular GC injection was recommended as an initial treatment option for patients with an AJC ≤4 (level C).
• Initiation of MTX or leflunomide was recommended for patients with an AJC >4 (level C).
• Initiation of NSAID monotherapy in a patient without prior treatment for a maximum period of 1 month was recommended as one treatment approach for patients with an AJC>0 (level D). Continuing NSAID monotherapy for longer than 2 months for patients with continued disease activity was in appropriate (level D).
• Anakinra was recommended as a therapeutic option for patients with an AJC >4 following failed intraarticular injection or NSAID monotherapy (level B). Use of anakinra was also recommended for patients with an AJC >0 following treatment with MTX or leflunomide (level B).
Initiation of canakinumab was recommended for patients with an AJC >4 only after a trial of a DMARD plus anakinra or tocilizumab (level B), a DMARD plus a TNF-inhibitor (level B) or abatacept (level C).

**Therapeutic Options for Continued Disease Activity:**
- Use of abatacept was recommended for patients with an AJC >0 after treatment with MTX or leflunomide (level B), anakinra (level D) or tocilizumab (level D).
- Anakinra was recommended as a therapeutic option for patients with an AJC >4 following failed intraarticular injection of NSAID monotherapy (level B). Use of anakinra was also recommended for patients with an AJC >0 following treatment with MTX or leflunomide (level B).
- Initiation of canakinumab was recommended for patients with an AJC >4 only after a trial of a DMARD plus anakinra or tocilizumab (level B), a DMARD plus a TNF-inhibitor (level B), or abatacept (level C).
- Use of MTX or leflunomide was recommended as an option for an AJC >0 following treatment with intraarticular injection (level C), NSAID monotherapy (level C), an IL-1 inhibitor (level D) or tocilizumab (level D).
- Initiation of a TNF inhibitor was recommended for patients with an AJC >0 after treatment with MTX or leflunomide (level C), anakinra (level D) or tocilizumab (level D).
- Initiation of tocilizumab was recommended for an AJC >0 following treatment with anakinra (level B) or MTX or leflunomide (level B).

**Systemic JIA with Features concerning for Macrophage Activation Syndrome (MAS):**

**Initial Therapeutic Options:**
- Use of anakinra was recommended as one therapeutic option for patients with features concerning for MAS (level C).
- Use of a calcineurin inhibitor was recommended as one therapeutic option for patients with features concerning for MAS (level C).
- Use of systemic GC monotherapy (administered by oral or intravenous route) was also recommended as a therapeutic option for patients with features concerning for MAS (level C).
- Continuing GC monotherapy for ≥2 weeks in patients with continued features concerning for MAS was inappropriate (level D).
Figure 3: Treatment pathways for patients with active systemic features and varying degrees of synovitis.
2013 Update of the 2011 American College of Rheumatology Recommendations for the Treatment of Juvenile Idiopathic Arthritis (JIA)
Figure 4: Treatment pathways for patients without active systemic features and with varying degrees of synovitis.
2013 Update of the 2011 American College of Rheumatology Recommendations for the Treatment of Juvenile Idiopathic Arthritis (JIA)
Patients with moderate to severe disease are treated with prednisone 40-60mg daily until resolution of symptoms and resumption of weight gain (generally 7-28 days) (grade A).

Azathioprine and 6-mercaptopurine are effective for maintaining a steroid-induced remission (grade A), and parenteral methotrexate at a dose of 25mg/week is effective for steroid-dependent and steroid-refractory CD (grade B).

The anti-TNF monoclonal antibodies, infliximab, adalimumab, and certolizumab-pegol are effective in the treatment of moderate to severe active CD in patients who have not responded despite complete and adequate therapy with a corticosteroid or an immunosuppressive agent (grade A).

Infliximab monotherapy and infliximab combined with azathioprine are more effective than azathioprine in the treatment of patients with moderate to severe CD who have failed to respond to first-line therapy with mesalamine and/or corticosteroids (grade A).

Infliximab, adalimumab, and certolizumab-pegol may be used as alternatives to steroid therapy in selected patients in whom corticosteroids are contraindicated or not desired (grade B).

The anti-alpha 4 integrin antibody, natalizumab, is effective in the treatment of patients with moderate to severely active CD who have had an inadequate response or are unable to tolerate conventional CD therapies and anti-TNF monoclonal antibody therapy (grade A).

**Entyvio (vedolizumab)**

Vedolizumab, a humanized anti-alpha-4-beta-7 integrin monoclonal antibody, was FDA-approved for induction and maintenance therapy in adults with moderately to severely active ulcerative colitis, and for achieving (but not maintaining) clinical response and remission in adults with moderately to severely active Crohn’s disease, who have had an inadequate response to at least one conventional therapy (e.g. TNF blocker, immunomodulator, glucocorticoids).

Crohn’s disease trial: In a double blind randomized trial, 368 patients were enrolled to receive either intravenous Entyvio (vedolizumab) or placebo. Concomitant stable dosages of aminosalicylates, corticosteroids (prednisone dosage ≤ 30mg/day or equivalent), and immunomodulators (azathioprine, 6-mercaptopurine or methotrexate) were permitted through Week 6. At week 6, 15% of patients taking Entyvio achieved clinically significant remission vs 7% with placebo (p= 0.041, primary end point). Nevertheless, there was no significant difference in CDAI-100 response (≥100 point decrease in CDAI score from baseline).

- In addition, maintenance of remission was assessed at week 52 by enrolling a total of 461 patients who demonstrated clinical response at week 6 in either the induction trial or the following open label group. At week 52, remission rates were significantly higher in the vedolizumab group (39%) vs placebo (22%) (p=0.001).

Ulcerative colitis trial: In a double blind randomized trial, 374 patients received either intravenous vedolizumab 300mg or placebo. Concomitant stable dosages of aminosalicylates, corticosteroids and immunomodulators (azathioprine or 6-mercaptopurine) were permitted through week 6. At week 6, the results demonstrated
statistically significant higher rates of clinical response in vedolizumab (47%) vs placebo (26%) (p<0.001). Furthermore, statistically significant higher rates of clinical remission, improvement of endoscopic appearance of the mucosa and corticosteroid-free remission at week 52 were observed in the vedolizumab group.

- However, vedolizumab was associated with an increased risk for developing serious infections. Although no cases of progressive multifocal leukoencephalopathy (PML) have been reported in clinical trials, death has occurred in patients treated with another integrin receptor antagonist. A risk of PML cannot be ruled out.

**2010 Ulcerative Colitis Practice Guidelines in Adults: American College of Gastroenterology, Practice Parameters Committee**

- Patients with mild to moderate distal colitis may be treated with oral aminosalicylates, topical mesalamine, or topical steroids (Evidence A).
- Topical mesalamine agents are superior to topical steroids or oral aminosalicylates (Evidence A).
- The combination of oral and topical aminosalicylates is more effective than either alone (Evidence A).
- The unusual patient who is refractory to all of the above agents at maximal doses, or who is systemically ill, may require treatment with oral prednisone in doses up to 40-60mg per day, or infliximab with an induction regimen of 5mg/kg at weeks 0, 2, and 6, although these two agents have not been studied specifically in patients with distal disease (Evidence C).
- Infliximab induction is an effective treatment for patients who are steroid refractory or steroid dependent despite adequate doses of a thiopurine, or who are intolerant to these medications. The infliximab induction dose is 5mg/kg given intravenously at weeks 0, 2, and 6 (Evidence A). Infliximab is contraindicated in patients with active infection, untreated latent TB, preexisting demyelinating disorder or optic neuritis, moderate to severe congestive heart failure, or current or recent malignancies.
- Infliximab is effective in maintaining improvement and remission in the patients responding to the infliximab induction regimen (Evidence A).
- The patient with severe colitis refractory to maximal oral treatment with prednisone, oral aminosalicylate drugs, and topical medications may be treated with infliximab 5mg/kg if urgent hospitalization is not necessary (Evidence A).
- Infliximab may also be effective in avoiding colectomy in patients failing intravenous steroids but its long-term efficacy is unknown in this setting (Evidence A).

**2011 American Academy of Dermatology Guidelines of Care for the Management of Psoriasis and Psoriatic Arthritis**

Psoriasis without Psoriatic Arthritis:

- Recommended first line topical agents include corticosteroids, calcipotriene, calcitriol, calcipotriene-steroid combination, tazarotene (preferably in combination with a topical steroid), calcineurin inhibitors (flexures and face).
UV therapy remains an important therapeutic option for patients with moderate to severe disease. It is effective in the majority of patients, is cost-effective, and lacks systemic toxicities and immunosuppressive properties of systemic and biological treatments.

Baseline screening, monitoring guidelines, absolute and relative contraindications, adverse events, and drug interactions of traditional systemic agents should be considered before initiating systemic agents.

MTX remains the most widely used, logical first choice of systemic agent, because it is the most cost-effective systemic psoriasis agent with the longest safety follow-up data. Adverse effects include gastrointestinal side effects, hepatotoxicity, bone marrow suppression, acute pneumonitis and pulmonary fibrosis.

Cyclosporine is particularly useful in the treatment of significant flares of psoriasis unresponsive to other therapies and as a bridging agent during the induction of other maintenance agents due to its rapid onset of action and marked efficacy. Intermittent short-term therapy with oral cyclosporine (12-16 weeks) is the most frequently recommended regimen, with treatment being withdrawn once significant improvement is achieved.

Biologic agents are now routinely used when one or more traditional systemic agents fail to produce an adequate response or are not tolerated because of the presence of comorbidities. There is no specific sequence in which the currently available TNF-α antagonists should be used.

Although the strength of recommendation A is noted for the treatment of psoriasis using ustekinumab, compared with the TNF-alfa inhibitors which have now been available for more than 10 years, there is limited post-marketing safety data on ustekinumab. Its safety information is supplied by pooled analysis of phase II and phase III clinical trials.

Psoriatic Arthritis:

- Mild PsA is most often managed with NSAIDs alone. If the psoriatic arthritis (PsA) is unresponsive after 2 to 3 months of therapy with NSAIDS, treatment with MTX should be considered.
- For patients with moderate to severe PsA, MTX, TNF-blockade, or combination of these therapies is considered first-line treatment. However, MTX is often used as first-line therapy before TNF-α blockade treatment, largely because of its significantly lower cost.
- Adalimumab, etanercept, golimumab and infliximab show similar efficacy for the signs and symptoms of PsA. On the other hand, infliximab clears cutaneous psoriasis in the highest proportion of patients and with the greatest rapidity, followed by adalimumab and then etanercept.

2015 European League Against Rheumatism recommendations for the Management of Psoriatic Arthritis with Pharmacological Therapies

- In patients with psoriatic arthritis, non-steroidal anti-inflammatory drugs may be used to relieve musculoskeletal signs and symptoms.
- In patients with peripheral arthritis, particularly in those with many swollen joint, structural damage in the presence of inflammation, high erythrocyte sedimentation rate/C reactive protein and/or clinically relevant extra-articular manifestations, csDMARDs
should be considered at an early stage, with MTX preferred in those with relevant skin involvement.

- Local injection of glucocorticoids should be considered as adjunctive therapy in PsA; systemic glucocorticoids may be used with caution at the lowest effective dose.
- In patients with peripheral arthritis and an inadequate response to at least one csDMARD, therapy with a bDMARD, usually a TNFi, should be commenced.
- In patients with peripheral arthritis and an inadequate response to at least one csDMARD, in whom TNFis are not appropriate, bDMARDs targeting interleukin (IL) 12/23 or IL-17 pathways may be considered.
- In patients with peripheral arthritis and an inadequate response to at least one csDMARD, in whom bDMARDs are not appropriate, a tsDMARD, such as a PDE4-inhibitor, may be considered.
- In patients with active enthesitis and/or dactylitis and insufficient response to NSAIDs or local glucocorticoid injections, therapy with a bDMARD should be considered, which according to current practice is a TNFi.
- In patients with predominantly axial disease that is active and has insufficient response to NSAIDs, therapy with a bDMARD should be considered, which according to current practice is a TNFi.
- In patients who fail to respond adequately to a bDMARD, switching to another bDMARD should be considered, including switching between TNFis.
Figure 5: 2015 EULAR Algorithm for Treatment of Psoriatic Arthritis
The primary goal of treating the patient with axSpA is to maximize long-term health-related quality of life through control of symptoms and inflammation, prevention of progressive structural damage, preservation/normalization of function and social participation.

The treatment of patients with axSpA should be individualized according to the current signs and symptoms of the disease (axial, peripheral, extra-articular manifestation) and the patient characteristics including comorbidities and psychosocial factors.

Disease monitoring of patients with axSpA should include patient-reported outcomes, clinical findings, laboratory tests and imaging, all with the appropriate instruments and relevant to the clinical presentation. The frequency of monitoring should be an individual basis depending on symptoms, severity and treatment.

Patient should be educated about axSpA and encouraged to exercise on a regular basis and stop smoking; physical therapy should be considered.

Patient suffering from pain and stiffness should use an NSAID as first-line drug treatment up to the maximum dose, taking risks and benefits into account. For patients who respond well to NSAIDs continuous use is preferred if symptomatic otherwise.

Analgesics, such as paracetamol and opioid-like drugs, might be considered for residual pain after previously recommended treatments have failed, are contraindicated and/or poorly tolerated.

Glucocorticoid injections directed to the local site of musculoskeletal inflammation may be considered. Patients with axial disease should not receive long-term treatment with systemic glucocorticoids.

Patients with purely axial disease should normally not be treated with csDMARDs; sulfasalazin may be considered in patients with peripheral arthritis.

bDMARDs should be considered in patients with persistently high disease activity despite conventional treatments; current practice is to start with TNFi therapy.

If TNFi therapy fails, switching to another TNFi or an anti-IL-17 therapy should be considered.

If a patient is in sustained remission, tapering of a bDMARD can be considered.

Inflectra (infliximab-dyyb)

The U.S. Food and Drug Administration approved Inflectra (infliximab-dyyb), a biosimilar to Remicade (infliximab) in April 5, 2016.

Inflectra is approved and can be prescribed by a health care professional for the treatment of:

- Adult patients and pediatric patients (ages six years and older) with moderately to severely active Crohn’s disease who have had an inadequate response to conventional therapy;
- Adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy;
- Patients with moderately to severely active rheumatoid arthritis in combination with methotrexate;
- Patients with active ankylosing spondylitis (arthritis of the spine);
- Patients with active psoriatic arthritis;
- Adult patients with chronic severe plaque psoriasis.

- The FDA’s approval of Inflectra is based on review of evidence that included structural and functional characterization, animal study data, human pharmacokinetic and pharmacodynamics data, clinical immunogenicity data and other clinical safety and effectiveness data that demonstrates Inflectra is biosimilar to Remicade. Inflectra has been approved as biosimilar, not as an interchangeable product.
- The most common expected side effects of Inflectra include respiratory infections, such as sinus infections and sore throat, headache, coughing and stomach pain. Infusion reactions can happen up to two hours after an infusion. Symptoms of infusion reactions may include fever, chills, chest pain, low blood pressure or high blood pressure, shortness of breath, rash and itching.
- Inflectra contains a Boxed Warning to alert health care professionals and patients about an increased risk of serious infections leading to hospitalization or death, including tuberculosis, bacterial sepsis, invasive fungal infections (such as histoplasmosis) and others. The Boxed Warning also notes that lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with tumor necrosis factor blockers, including infliximab products such as Inflectra. Other serious side effects may include liver injury, blood problems, lupus-like syndrome, psoriasis, and in rare cases nervous system disorders. The drug must be dispensed with a patient Medication Guide that describes important information about its uses and risks.

**Xeljanz (tofacitinib)**

Xeljanz (tofacitinib), a janus kinase (JAK) inhibitor, interferes with the JAK-STAT signaling pathway and therefore the development of inflammation associated with rheumatoid arthritis. Fleischmann et al (2012) conducted a phase 3, double-blind, placebo-controlled, parallel-group, 6 month study. Patients (n = 611) were randomly assigned to tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, 3 months of placebo and 3 months of tofacitinib 5 mg twice daily, or 3 months of placebo and tofacitinib 10 mg twice daily. The three primary endpoints were a 20% improvement in the American College of Rheumatology scale (ACR 20), change from baseline in the Health Assessment Questionnaire–Disability Index (HAQ-DI) score (score range from 0 to 3), and percentage of patients with a Disease Activity Score for 28-joint counts of less than 2.6 (score range from 0 to 9.4) based on the erythrocyte sedimentation rate (DAS28-4[ESR]). By month 3, patients in the tofacitinib groups had a higher percentage of improvement in the ACR20 (p < 0.001) and greater reductions from baseline in the HAQ-DI score (p <0.001). The percentage of patients with a DAS28-4[ESR] less than 2.6 was not significantly greater in the tofacitinib groups, 5 mg and 10 mg, compared to placebo (p = 0.62 and p = 0.10, respectively). Six patients receiving tofacitinib developed serious infections. Tofacitinib treatment was associated with increased levels of low-density lipoprotein (LDL) cholesterol levels and decreased neutrophil counts. Common adverse events included headache and upper respiratory tract infections.
In a 12 month, phase III clinical trial, van Vollenhoven et al (2012) compared tofacitinib and adalimumab in patients who were receiving methotrexate. Patients \( n = 717 \) were randomly assigned to tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, adalimumab 40 mg every 2 weeks, or placebo. Those who did not receive a 20% reduction from baseline in the number of swollen and tender joints were transitioned to either tofacitinib 5 mg or 10 mg at month 3 and month 6. The three primary endpoints were a 20% improvement at months 6 in the American College of Rheumatology scale (ACR 20), change from baseline to month 3 in the Health Assessment Questionnaire–Disability Index (HAQ-DI) score (score range from 0 to 3), and percentage of patients at month 6 who had a Disease Activity Score for 28-joint counts of less than 2.6 (score range from 0 to 9.4) based on the erythrocyte sedimentation rate (DAS28-4[ESR]). At month 6, the ACR 20 response rates were higher among the tofacitinib and adalimumab groups compared to placebo \( p < 0.001 \). In addition, the percentage of patients with a DAS28-4[ESR] below 2.6 in both active treating groups was higher than placebo. At month 3, reductions in the HAQ-DI were greater among the tofacitinib and adalimumab groups compared to placebo. Adverse events were found more frequently with tofacitinib than placebo. While tofacitinib demonstrated superiority to placebo, the study was not designed to directly evaluate the efficacy of tofacitinib compared to adalimumab.

Currently, studies have not shown any biologic DMARDs or JAK-inhibitor, tofacitinib, to be more effective than another in the treatment of rheumatoid arthritis. However, the safety profile for tofacitinib is limited relative to other alternatives. During clinical trials, tofacitinib was associated with an increased risk of serious infections, including opportunistic infections, tuberculosis, cancers and lymphoma. The most common adverse effects were upper respiratory tract infections, headache, diarrhea, and inflammation of the nasal passage and the upper part of the pharynx.

References:


<table>
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<tr>
<td>08/16/2017</td>
<td>• Added Renflexis (biosimilar to Remicade) as NF preferred over Inflectra for Crohn’s/Ulcerative Collitis when billed as pharmacy benefit. On parity with Inflectra for Crohn’s/Ulcerative Collitis when billed as a medical benefit.</td>
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<td></td>
<td>• Revised criteria for Crohn’s/Ulcerative Collitis and added re-authorization criteria</td>
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<tr>
<td></td>
<td>• Added criteria and re-authorization criteria for Ilaris</td>
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