Drug Class Monograph

Class: Therapeutic Agents in Rheumatic and Inflammatory Diseases

Drug: Actemra (tocilizumab), Cimzia (certolizumab), Cosentyx (secukinumab), Enbrel (etanercept), Entyvio (vedolizumab), Humira (adalimumab), Inflectra (infliximab-dyyb), Kineret (anakinra), Orencia (abatacept), Otezla (apremilast), Remicade (infliximab), Simponi, Simponi Aria (golimumab), Stelara (ustekinumab), Xeljanz (tofacitinib)

Line of Business: Non-Medicare
Effective Date: November 16, 2016
Renewal Date: November 16, 2016

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.

Policy/Criteria:

1. Rheumatoid Arthritis:

Actemra (tocilizumab), Cimzia (certolizumab), Cosentyx (secukinumab), Enbrel (etanercept), Humira (adalimumab), Inflectra (infliximab-dyyb), Kineret (anakinra), Orencia (abatacept), Remicade (infliximab), Simponi, Simponi Aria (golimumab), Xeljanz (tofacitinib)

Medication is considered medically necessary if the following criteria are met:

   a. Diagnosis of Rheumatoid Arthritis;
   b. Prescribed by a rheumatologist;
   c. Inadequate response to at least one DMARD (e.g. methotrexate, sulfasalazine, hydroxychloroquine, leflunomide, etc.);
   d. Formulary Position: Enbrel (etanercept) & Humira (adalimumab) are the preferred agents for Rheumatoid Arthritis (RA).

2. Crohn’s Disease:

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

Medication is considered medically necessary if the following criteria are met:

   a. Confirmed diagnosis of Crohn’s Disease;
b. Patient must have inadequate response to two of the following conventional therapy:
   • Aminosalicylates (e.g. mesalamine, sulfasalazine);
   • Immunosuppressive Agents (e.g. azathioprine, mercaptopurine or methotrexate);
   • Corticosteroids (e.g. prednisone);

c. Prescribed by GI specialist;

d. **Formulary Position:** Humira (adalimumab) is the preferred agent for Crohn’s Disease, then Cimzia (certolizumab), then Inflectra (infliximab-dyyb).

3. Ulcerative Colitis:

**Entyvio (vedolizumab), Humira (adalimumab), Inflectra (infliximab-dyyb), Remicade (infliximab), Simponi (golimumab)**
Medication is considered medically necessary if the following criteria are met:

a. Confirmed diagnosis of ulcerative colitis;

b. Patient must have inadequate response to the following conventional therapy:
   • Aminosalicylates (e.g. balsalazide, mesalamine, sulfasalazine)
   • Immunosuppressive Agents (e.g. azathioprine, 6-mercaptopurine) or corticosteroids (e.g. budesonide, prednisone);

c. Prescribed by GI specialist;

d. **Formulary Position:** Humira (adalimumab) is the preferred agent for ulcerative colitis, then Simponi (golimumab), then Inflectra (infliximab-dyyb).

4. Plaque Psoriasis without Psoriatic Arthritis:

**Cosentyx (secukinumab), Enbrel (etanercept), Humira (adalimumab), Inflectra (infliximab-dyyb), Remicade (infliximab), Stelara (ustekinumab)**
Medication is considered medically necessary if the following criteria are met:

a. Confirmed diagnosis of plaque psoriasis;

b. Patient must have inadequate response to ultraviolet therapy (PUVA or UVB) OR at least one (1) DMARD within the last year (12 months);

c. Prescribed by a dermatologist;

d. **Formulary Position:** Enbrel (etanercept) & Humira (adalimumab) are the preferred agents for Plaque Psoriasis. Non-TNF agents may be considered medically necessary if patient has contraindication or risk for serious adverse effect to TNF inhibitors (e.g. demyelinating disease, multiple sclerosis, malignancy, heart failure, etc.).
**Otezla (apremilast)**
Medication is considered medically necessary if the following criteria are met:

- a. Confirmed diagnosis of plaque psoriasis and/or psoriatic arthritis;
- b. Patient must have inadequate response to ultraviolet therapy (PUVA or UVB) OR at least one (1) DMARD within the last year (12 months);
- c. Prescribed by a dermatologist or rheumatologist;
- d. Failure or clinically significant adverse effects to Enbrel or Humira.

5. **Psoriatic Arthritis:**

**Cimzia (certolizumab), Enbrel (etanercept), Humira (adalimumab), Inflectra (infliximab-dyyb), Remicade (infliximab), Simponi (golimumab), Stelara (ustekinumab)**
Medication is considered medically necessary if the following criteria are met:

- a. Confirmed diagnosis of psoriatic arthritis;
- b. Prescribed by a dermatologist or rheumatologist;
- c. One of the following:
  - Documented inadequate response to one DMARD within the last year (12 months);
- e. **Formulary Position:** Enbrel (etanercept) & Humira (adalimumab) are the preferred agents for Psoriatic Arthritis. Non-TNF agents may be considered medically necessary if patient has contraindication or risk for serious adverse effect to TNF inhibitors (e.g. demyelinating disease, multiple sclerosis, malignancy, heart failure, etc.).

6. **Ankylosing Spondylitis:**

**Cimzia (certolizumab), Enbrel (etanercept), Humira (adalimumab), Inflectra (infliximab-dyyb), Remicade (infliximab), Simponi (golimumab)**
Medication is considered medically necessary if the following criteria are met:

- a. Confirmed diagnosis of ankylosing spondylitis;
- b. Patient must have had inadequate response to one formulary NSAID;
- c. Patient must be at least 18 years of age;
- d. Prescribed by a rheumatologist;
- e. **Formulary Position:** Enbrel (etanercept) & Humira (adalimumab) are the preferred agents for Ankylosing Spondylitis.
Clinical Evidence:

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

Recommendation for the treatment of patients with early RA:

<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>
</tbody>
</table>
| 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). | Low (18-21)  
Low (22-25) |
| 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). | Moderate (18, 20, 21)  
High (22-25) |
| 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). | Low (26-28) |
| 5. If disease activity remains moderate or high despite DMARDs:  
  - use a TNFi monotherapy over tofacitinib monotherapy (PICO A.8).  
  - use a TNFi + MTX over tofacitinib + MTX (PICO A.9). | Low (29)  
Low (30) |
| 6. If disease activity remains moderate or high despite DMARD (PICO A.6) or biologic therapies (PICO A.12), add low-dose glucocorticoids. | Moderate (31-37)  
Low (31-37) |
| 7. If disease flares, add short-term glucocorticoids at the lowest possible dose and for the shortest possible duration (PICO A.10, A.11). | Very low (38-43) |
2015 American College of Rheumatology recommendations update for the treatment of early rheumatoid arthritis (RA) defined as a disease duration < 6 months.
Recommendation for the treatment of patients with established RA:

<table>
<thead>
<tr>
<th>Recommendations for patients with Established 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 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 (23,26,29,36,47,48,50-59) |
| 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^5 |
| 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^5 |
| 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) ^6,  
  - taper TNFI, non-TNF biologic, or tofacitinib (PICO B.33, B.35, B.37) (please also see #15). | Low^6 (78)  
 Moderate to Very low^6 (75,80) |
| 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^4 |
Figure 2: 2012 American College of Rheumatology (ACR) recommendations update for the treatment of established rheumatoid arthritis (RA) defined as a disease duration ≥6 months
Recommendation in RA patients with high-risk comorbidities:

<table>
<thead>
<tr>
<th>High-risk condition</th>
<th>Recommendation</th>
<th>Level of Evidence (Evidence reviewed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure</td>
<td>Use combination DMARDs or non-TNF biologic or tocilizumab 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 tocilizumab over another TNFi (PICO C.4, C.5 and C.6).</td>
<td>Very low</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Same recommendations as in patients without this condition (PICO D.1).</td>
<td>Very low (85-92)</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>Same recommendations as in patients without this condition (PICO E.1).</td>
<td>Very low (92-103)</td>
</tr>
<tr>
<td>Hepatitis C infection and not receiving or 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></td>
<td></td>
</tr>
<tr>
<td>Previously treated or untreated skin cancer (non-melanoma or melanoma)</td>
<td>Use DMARDs over biologics in melanoma (PICO F.1); Use DMARDs over tocilizumab in melanoma (PICO F.2).</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>

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 (Kineret) was recommended as one initial therapeutic option for patients with an MD global ≥5 irrespective of the active joint count (AJC), or a physician global assessment (MD global) <5 and an AJC >0 (level C)
- Systemic 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).
• 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 (Kineret) 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 (Actemra) 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 patient 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).
• MTX or leflunomide was recommended for patients with an MD global <5 and an AJC >0 after treatment with GC monotherapy (level C), an IL-1 inhibitor [e.g. anakinra (Kineret)] (level D) or tocilizumab (Actemra) (level D).
• 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)
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)
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)
2009 American College of Gastroenterology Practice Guidelines: Management of Crohn’s Disease in Adults

- 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 clinical 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 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 of 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. As a result, at week 6, statically 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 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 in 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 the latter 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 of these medications. The infliximab induction dose is 5mg/kg intravenously at weeks 0, 2, and 6 weeks (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 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, are not tolerated because of the presence of comorbidities. There is no specific sequence in which the currently available TNF-alfa 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, mostly limited to pooled analysis of phase II and phase III clinical trials.

Psoriatic Arthritis:

- Mild PsA is most often managed with NSAIDs alone. If the 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-alfa 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.

2012 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 (Level of Evidence 1B).
- In patients with active disease (particularly those with many swollen joints, structural damage in the presence of inflammation, high ESR/CRP and/or clinically relevant extraarticular manifestations), treatment with disease-modifying drugs, such as methotrexate, sulfasalazine, leflunomide, should be considered at an early stage (Level of Evidence 1B).
- In patients with active psoriatic arthritis and clinically relevant psoriasis, a disease-modifying drug that also improves psoriasis, such as methotrexate, should be preferred (Level of Evidence 1B).
- Local injections of corticosteroids should be considered as adjunctive therapy in psoriatic arthritis; systemic steroids at the lowest effective dose may be used with caution (Level of Evidence 3B).
• In patients with active arthritis and an inadequate response to at least one synthetic disease-modifying antirheumatic drug, such as methotrexate, therapy with a tumor necrosis factor inhibitor should be commenced (Level of Evidence 1B).
• In patients with active enthesitis and/or dactylitis and insufficient response to non-steroidal anti-inflammatory drugs or local steroid injections, tumor necrosis factor inhibitors may be considered (Level of Evidence 1B).
• In patients with predominantly axial disease that is active and has insufficient response to non-steroidal anti-inflammatory drugs, tumor necrosis factor inhibitors should be considered (Level of Evidence 2B).
• Tumor necrosis factor inhibitor therapy might exceptionally be considered for a very active patient naive of disease-modifying treatment (particularly those with many swollen joints, structural damage in the presence of inflammation, and/or clinically relevant extra-articular manifestations, especially extensive skin involvement) (Level of Evidence 4).
• In patients who fail to respond adequately to one tumor necrosis factor inhibitor, switching to another tumor necrosis factor inhibitor should be considered (Level of Evidence 2B).

2010 Update of the ASAS/EULAR Recommendations for the Management of Ankylosing Spondylitis

• The treatment of patients with AS should be tailored according to the current manifestation of the disease, level of current symptoms, clinical findings, prognostic indicators and general clinical status.
• The optimal management of patients with AS requires a combination of non-pharmacological and pharmacological treatment modalities.
• NSAID, including Coxibs, are recommended as first line drug treatment for AS patients with pain and stiffness.
• Analgesics, such as opioid like drug, might be considered for residual pain after previously recommended treatment have failed, are contraindicated, and/or poorly tolerated.
• Corticosteroid injections directed to the local site of musculoskeletal inflammation may be considered. The use of systemic corticosteroids for axial disease is not supported by evidence.
• There is no evidence for efficacy of DMARD, including sulphasalazine and methotrexate, for the treatment of axial disease. Sulfasalazine may be considered in patients with peripheral arthritis.
• Anti-TNF therapy should be given to patients with persistently high disease activity despite conventional treatments according to the ASAS recommendations.
  o There is no evidence to support the obligatory use of DMARD before or concomitant with anti-TNF therapy in patients with axial disease.
  o There is no evidence to support a difference in efficacy of the various TNF inhibitors on the axial and articular enthesal disease manifestations; but in the presence of IBD a difference in gastrointestinal efficacy needs to be taken into account.
  o Switching to a second TNF blocker might be beneficial especially in patients with loss of response.
  o There is no evidence to support the use of biological agents other than TNF inhibitors in AS.
**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:

Recommendations for the Use of Disease-Modifying Antirheumatic Drugs and Biologic Agents in the
Treatment of Rheumatoid Arthritis. Arthritis Care & Research Vol. 64, No. 5, May 2012:625-639
29. American College of Rheumatology Ad Hoc Committee on Clinical Guidelines. Guidelines for the initial
30. American College of Rheumatology Ad Hoc Committee on Clinical Guidelines. Guidelines for the
31. American College of Rheumatology Ad Hoc Committee on Clinical Guidelines. Guidelines for the
32. American College of Rheumatology Ad Hoc Committee on Clinical Guidelines. Guidelines for monitoring
35. Maini RN, Breedveld FC, Kalden JR, Smolen JS, Davis D, Macfarlane JD, et al. Therapeutic efficacy of
multiple intravenous infusions of anti–tumor necrosis factor monoclonal anti-body combined with low-dose
carcinomatous factor monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant
Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. Infliximab and
recombinant tumor necrosis factor receptor:Fc fusion protein, in patients with rheumatoid arthritis receiving
monoclonal antibody treatment of patients with rheumatoid arthritis receiving methotrexate therapy. J Rheumatol
41. Moreland LW, Cohen SB, Baumgartner S, Schiff M, Tindall EA, Burdge DJ. Long-term use of etanercept in
43. Felson DT, Anderson JJ, Meenan RF. The comparative efficacy and toxicity of second-line drugs in
44. Wells G, Haguenauer D, Shea B, Suarez-Almazor ME, Welch A, Tugwell P. Cyclosporine for treating
45. Haagsma CJ, van Reil PL, de Jong AJ, van de Putte LB. Combination of sulfasalazine and methotrexate


