Infusible Biologics Medical Policy
Prior Authorization

Program Summary

The BCBS AL Continuation of Therapy policy applies to this medical policy.

OBJECTIVE
The intent of the Infusible Biologics program is to ensure that patients prescribed therapy are properly selected according to Food and Drug Administration (FDA)-approved product labeling and/or clinical guidelines and/or clinical trials. The criteria will encourage the use of first-line conventional agents, some of which are available as generics (for example, first-line agents for arthritis indications, methotrexate and leflunomide, are both available as generics). Criteria will require a FDA approved diagnosis and the use of a conventional agent before use of the agents listed below. Because there are no studies supporting concomitant therapy with any two of these agents or with Otezla, and because combinations of biologics have resulted in increases in serious infections, criteria will allow coverage of only one biologic immunomodulator at a time and will not allow concomitant use with Otezla. The program will approve Actemra, Cimzia, Entyvio, Orencia, Simponi ARIA, or Stelara for doses within FDA approved dosing. Doses above FDA approved dosing will be approved if the prescriber has submitted documentation in support of therapy with a higher dose for the intended diagnosis.

Target Agents
Actemra® (tocilizumab)
Cimzia® (certolizumab)
Entyvio® (vedolizumab)
Orencia® (abatacept)
Simponi ARIA® (golimumab)
Stelara® (ustekinumab)

Initial Evaluation
Actemra, Cimzia, Entyvio, Orencia, Simponi ARIA, or Stelara will be approved when following are met:
1. ALL of the following:
   i. ONE of the following:
      a. The patient has an FDA labeled indication for the requested agent
      OR
      b. The patient has an FDA labeled diagnosis for the requested agent however the patient’s age is outside of FDA labeling and the prescriber attests treatment is clinically appropriate
   AND
   ii. ONE of the following:
      a. The patient’s medication history indicates use of another biologic immunomodulator agent or Otezla for the same FDA labeled indication
      OR
      b. The patient’s diagnosis does not require a conventional agent prerequisite*
      OR
      c. The patient’s medication history indicates use of one conventional agent prerequisite*
      OR
      d. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to at least ONE conventional agent
iii. If Stelara 90 mg is requested, ONE of the following:
   a. The patient has a diagnosis of psoriasis AND weighs >100kg AND the patient has failed (had an inadequate response to) a trial of 45mg for at least 3 months OR
   b. The patient has a dual diagnosis of psoriasis AND psoriatic arthritis AND the patient is >100kg OR
   c. The patient has a diagnosis of Crohn's disease

iv. The patient is not currently being treated with another biologic immunomodulator agent or Otezla

v. The patient does not have any FDA labeled contraindication(s) to therapy with the requested agent

vi. The patient has been tested for latent TB when required by the prescribing information AND if positive the patient has begun therapy for active TB

2. ONE of the following:
   i. The prescribed dosage is within FDA labeled dosing OR
   ii. The quantity (dose) requested is greater than the maximum dose recommended in FDA labeling, and the prescriber has submitted documentation in support of therapy with a higher dose for the intended diagnosis which has been reviewed and approved

Length of Approval: 12 months for all agents EXCEPT Actemra (tocilizumab) for Cytokine Release Syndrome (CRS), Entyvio (vedolizumab) and Stelara (ustekinumab) IV. Initial approval for Actemra for CRS is a one time approval for up to 4 doses in 1 month. Initial approval for Entyvio is 4 months and Stelara IV is 3 months.

Renewal Evaluation
1. The patient has been previously approved for therapy through Prime Therapeutics Medical Drug Review process

AND

2. The patient has shown clinical improvement (e.g. slowing of disease progression or decrease in symptom severity and/or frequency)

AND

3. If Stelara 90 mg is requested, ONE of the following:
   i. The patient has a diagnosis of psoriasis AND weighs >100kg AND the patient has failed (had an inadequate response to) a trial of 45mg for at least 3 months OR
   ii. The patient has a dual diagnosis of psoriasis AND psoriatic arthritis AND the patient is >100kg OR
   iii. The patient has a diagnosis of Crohn’s disease

4. The patient does not have any FDA labeled contraindications to the requested agent

AND

5. The patient is not currently being treated with another biologic immunomodulator or Otezla

AND

6. ONE of the following:
   i. The prescribed dosage is within FDA labeled dosing OR
   ii. The quantity (dose) requested is greater than the maximum dose recommended in FDA approved labeling, and the prescriber has submitted documentation in support of therapy with a higher dose for the intended diagnosis which has been reviewed and approved

Length of Approval: 12 months
<table>
<thead>
<tr>
<th>Target Agent</th>
<th>FDA Labeled Indications</th>
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<tbody>
<tr>
<td>Actemra (tocilizumab)</td>
<td>RA, SJIA, PJIA, GCA, CRS</td>
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<tr>
<td>Cimzia (certolizumab)</td>
<td>RA, CD, PSA, AS</td>
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<td>Cosentyx (secukinumab)</td>
<td>PS, PSA, AS</td>
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<tr>
<td>Enbrel (etanercept)</td>
<td>RA, PJIA, PSA, AS, PS</td>
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<tr>
<td>Entyvio (vedolizumab)</td>
<td>UC, CD</td>
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<tr>
<td>Humira (adalimumab)</td>
<td>RA, PJIA, PSA, AS, PS, CD, UC, HS,Uveitis</td>
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<td>Inflectra (infliximab-dyyb)</td>
<td>RA, PSA, AS, PS, CD, UC</td>
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<tr>
<td>Kevzara (sarilumab)</td>
<td>RA</td>
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<td>Kineret (anakinra)</td>
<td>RA, CAPS/NOMID</td>
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<td>Orencia (abatacept)</td>
<td>RA, PJIA, PSA</td>
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<td>Otezla (apremilast)</td>
<td>PSA, PS</td>
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<td>Remicade (infliximab)</td>
<td>RA, PSA, AS, PS, CD, UC</td>
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<td>Renflexis (infliximab-abda)</td>
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<td>Rituxan (rituximab)</td>
<td>RA, CLL, NHL, WG/MPA</td>
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<td>Siliq (brodalumab)</td>
<td>PS</td>
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<td>Simponi (golimumab)</td>
<td>RA, PSA, AS, UC</td>
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<tr>
<td>Simponi ARIA (golimumab)</td>
<td>RA, PSA, AS</td>
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<tr>
<td>Stelara (ustekinumab)</td>
<td>CD, PS</td>
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<tr>
<td>Taltz (ixekizumab)</td>
<td>PS</td>
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<td>Tremfya (guselkumab)</td>
<td>PS</td>
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<tr>
<td>Xeljanz (tofacitinib) and Xeljanz XR (tofacitinib extended release)</td>
<td>PSA, RA</td>
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AS=Ankylosing Spondylitis, CAPS/NOMID=Cryopyrin Associated Periodic Syndrome/Neonatal-Onset Multisystem Inflammatory Disease, CD=Crohn’s Disease, CLL=Chronic Lymphocytic Leukemia, CRS = Cytokine Release Syndrome, DMARD=Disease Modifying Antirheumatic Drug, GCA=Giant Cell Arteritis, HS=Hidradenitis Suppurativa, JIA=Juvenile Idiopathic Arthritis, MTX=methotrexate, NHL=Non-Hodgkin Lymphoma, PJJIA=Polavarticular Juvenile Idiopathic Arthritis, PSA=Psoriasis, RA=Rheumatoid Arthritis, SJIA=Systemic Juvenile Idiopathic Arthritis, UC=Ulcerative Colitis, WG/MPA=Wegener’s Granulomatosis/Microscopic Polyangiitis

*Conventional Agent Prerequisites by Indication*

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<thead>
<tr>
<th>FDA Labeled Indications</th>
<th>Conventional Agent Prerequisites</th>
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<tbody>
<tr>
<td>Rheumatoid arthritis (RA)</td>
<td>methotrexate, leflunomide, minocycline, sulfasalazine, hydroxychloroquine</td>
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<tr>
<td>Polyarticular Juvenile idiopathic arthritis (PJJIA)</td>
<td>anthralin, calcipotriene, calcitriol, acitretin, tazarotene, cyclosporine, methoxsalen, tacrolimus, pimecrolimus, PUVA (phototherapy)</td>
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<tr>
<td>Systemic juvenile idiopathic arthritis (SJIA)</td>
<td>methotrexate, topical corticosteroids, coal tar products</td>
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<tr>
<td>Psoriatic arthritis (PSA)</td>
<td>methotrexate, hydroxychloroquine, methotrexate, topical corticosteroids, coal tar products, anthralin, calcipotriene, calcitriol, acitretin, tazarotene, cyclosporine, methoxsalen, tacrolimus, pimecrolimus, PUVA (phototherapy)</td>
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<tr>
<td>Psoriasis (PS)</td>
<td>methotrexate, topical corticosteroids, coal tar products, anthralin, calcipotriene, calcitriol, acitretin, tazarotene, cyclosporine, methoxsalen, tacrolimus, pimecrolimus, PUVA (phototherapy)</td>
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<tr>
<td>Crohn’s disease (CD)</td>
<td>methotrexate, aminosalicylates</td>
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<tr>
<td>Ulcerative colitis (UC)</td>
<td>methotrexate, hydroxychloroquine, methotrexate, topical corticosteroids, coal tar products, anthralin, calcipotriene, calcitriol, acitretin, tazarotene, cyclosporine, methoxsalen, tacrolimus, pimecrolimus, PUVA (phototherapy)</td>
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<td><strong>FDA Labeled Indications</strong></td>
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<td>corticosteroids (including budesonide</td>
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<td>EC capsule)</td>
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<td>cyclosporine</td>
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<td>azathioprine</td>
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<td>6-mercaptopurine</td>
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<td>metronidazole</td>
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<td></td>
<td>ciprofloxacin</td>
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<tr>
<td>Giant Cell Arteritis (GCA)</td>
<td>systemic corticosteroid therapy (e.g.,</td>
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<td></td>
<td>prednisone, methylprednisolone)</td>
</tr>
<tr>
<td>Ankylosing spondylitis (AS)</td>
<td>None required</td>
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<tr>
<td>Cytokine Release Syndrome (CRS)</td>
<td>None required</td>
</tr>
</tbody>
</table>

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<tr>
<th>Agent</th>
<th>FDA Labeled Indications</th>
<th>Dosing</th>
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| Actemra (tocilizumab)*| RA – inadequate response to 1 or more DMARDS  
PJIA – in patients 2 years or older  
SJIA – in patients 2 years or older  
GCA CRS – in patients 2 years or older with chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome (CRS) | RA - 4-8 mg/kg every 4 weeks. Not to exceed 800 mg per infusion  
SC - 162 mg weekly  
PJIA - 10 mg/kg for those < 30 kg  
8 mg/kg for those ≥ 30 kg  
Every 4 weeks  
SJIA - 12 mg/kg for those < 30 kg  
8 mg/kg for those ≥ 30 kg every 2 weeks  
GCA - 162 mg SC every week. Every other week can be used based on clinical considerations  
CRS (only IV) - <30kg weight: 12 mg/kg (not to exceed 800mg per infusion)  
≥30 kg weight: 8 mg/kg (not to exceed 800mg per infusion)  
If no clinical improvement in signs/symptoms of CRS after the 1st dose, up to 3 additional doses, at least 8 hours apart, may be administered |
| Cimzia (certolizumab) | Crohn’s disease with inadequate response to conventional therapy  
RA  
PsA  
AS | CD: - 400 mg Week 0, 2, and 4. Then 400 mg every 4 weeks  
RA – 400 mg Week 0, 2, and 4, then 200 mg every other week or 400 mg every 4 weeks  
PsA – 400 mg Week 0, 2, and 4, then 200 mg every other week or 400 mg every 4 weeks  
AS – 400 mg Week 0, 2, and 4, then 200 mg every other week or 400 mg every 4 weeks |
| Entyvio (vedolizumab)#| CD - after inadequate response, loss of response, or intolerance to TNF or immunomodulator or corticosteroid dependence with loss of response, inadequate response, or intolerance  
UC – after inadequate response, loss of response, or intolerance to TNF or immunomodulator or corticosteroid dependence with loss of response, inadequate response, or intolerance | CD - 300 mg IV week 0, 2, and 6, then every 8 weeks  
UC - 300 mg IV week 0, 2, and 6, then every 8 weeks |
| Oencia (abatacept)   | RA – monotherapy or in combo with non-TNF DMARD  
PJIA – 2 years or older (IV- ≥6 y.o.; SC- ≥2 y.o.) as monotherapy or in combo with MTX  
PsA | RA – 500 mg if weight <60kg, 750 mg if between 60-100kg, 1000 mg if >100 kg at week 0, week 2, and week 4, then every 4 weeks;  
SC - 125 mg once weekly with or without initial IV loading dose |
PJIA – IV 10 mg/kg < 75 kg. ≥75 kg receive adult IV dose (see IV dosing for RA) up to 1000 mg at week 0, week 2, and week 4, then every 4 weeks SC- 10-<25 kg= 50 mg SC once weekly; 25-<50 kg= 87.5 mg SC once weekly; ≥50 kg= 125 mg SC once weekly
PsA – SC 125 mg once weekly without the need of an initial IV loading dose

| Simponi ARIA (golimumab) | RA - In combo with MTX, does not require failure of other DMARDS AS PsA | RA, PsA, AS - 2 mg/kg at weeks 0 and 4, then every 8 weeks. |
| Simponi (golimumab) | Ps (≥12 yrs) – who are candidates for phototherapy or systemic therapy PsA – monotherapy or in combo with MTX CD – failed or were intolerant to treatment with immunomodulators or corticosteroids, but never failed a tumor necrosis factor (TNF) blocker OR failed or were intolerant to treatment with one or more TNF blockers |
| Stelara (ustekinumab)^ | PsA – monotherapy or in combo with MTX CD – failed or were intolerant to treatment with immunomodulators or corticosteroids, but never failed a tumor necrosis factor (TNF) blocker OR failed or were intolerant to treatment with one or more TNF blockers |

Abbreviations:
- AS=Ankylosing Spondylitis
- CD=Crohn’s Disease
- CRS=Cytokine Release Syndrome
- DMARD=disease modifying antirheumatic drug
- GCA=Giant Cell Arteritis
- JIA=Juvenile Idiopathic Arthritis
- MTX=methotrexate
- PJIA=Polyarticular Juvenile Idiopathic Arthritis
- Ps=Psoriasis
- PsA=Psoriatic Arthritis
- RA=Rheumatoid Arthritis
- SJIA=systemic juvenile idiopathic arthritis
- UC=Ulcerative Colitis

*It is recommended that ACTEMRA not be initiated in patients with an absolute neutrophil count (ANC) below 2000 per mm3, platelet count below 100,000 per mm3, or who have ALT or AST above 1.5 times the upper limit of normal (ULN).
ACTEMRA doses exceeding 800 mg per infusion are not recommended in RA patients
#discontinue if no therapeutic benefit by week 14
^^for co-existent moderate-to-severe plaque psoriasis > 100 kg, dose is 90 mg initially then 4 weeks later, followed by 90 mg every 12 weeks
‡ Labeling supports efficacy in patients weighing > 100 kg at the 45 mg dose but notes greater efficacy in those patients at the 90 mg dose. In 2 clinical outcomes studies patients weighing > 100 kg and were randomized to the 45 mg dose of Stelara or the 90 mg dose of Stelara. Of those patients on the 45 mg dose 54% and 49% had a PASI 75 response compared to 68% and 71% PASI 75 response at the 90 mg dose of Stelara at week 12. In subjects weighing > 100 kg, 45 mg was shown to be efficacious.
∞ - A single weight-based intravenous induction dose is as follows: ≤55 kg- 260 mg (2 vials); >55 kg to 85 kg- 390 mg (3 vials); >85 kg- 520 mg (4 vials).

**CLINICAL RATIONALE**

**Rheumatoid arthritis (RA)**
American College of Rheumatology guidelines (2015) support a treat-to-target approach in therapy. The guidelines categorize therapy for those with recent diagnosis (<6 months) and those with an established diagnosis (> 6 months) and the severity within these two divisions. ACR recommends methotrexate unless...
contraindicated to all RA patients regardless of disease duration or severity. In patients with RA <6 months with moderate-high disease activity with poor prognosis DMARD combination therapy or a TNF antagonist with or without MTX, or non-TNF with or without MTX is recommended. Those with RA > 6 months that fail DMARD monotherapy, combination DMARD use, TNF inhibitor ± MTX, non-TNF ± MTX, or tofacitinib ± MTX can be used. The EULAR (2013) update, echoes the ACR suggesting MTX is the preferred 1st line conventional agent (sulfasalazine or leflunomide when MTX is inappropriate). After failure to MTX, a patient with no poor prognostic factors present should change the DMARD or initiate DMARD combination therapy prior to biologic therapy. A patient with poor prognostic factors warrants the addition of a biologic reiterating that MTX has been failed prior (unless clinically inappropriate).

Systemic onset juvenile idiopathic arthritis (SJIA)
Systemic onset juvenile idiopathic arthritis (SJIA) was formerly called Still’s disease and is a subset of juvenile idiopathic arthritis (JIA) that describes patients with fever, rash, and arthritis. The American College of Rheumatology (ACR) 2013 SJIA initial therapy treatment update for active systemic features includes nonsteroidal antiinflammatory drugs (NSAIDs), systemic glucocorticoids (oral or intravenous) and Anakinra (IL-1). Many children with SJIA have refractory disease, in which agents targeting interleukins IL-1 and IL-6 are used. ACR suggests continued disease activity be managed with canakinumab (IL-1), tocilizumab (IL-6), TNF-α inhibitors, methotrexate, leflunomide or options included in initial therapy not yet utilized. Treatment suggestions/decisions are based on the patient’s physician global assessment (MD global) and active joint count (AJC).

Psoriasis and Psoriatic Arthritis (PsA)
The American Academy of Dermatology guidelines state that 80% of psoriasis patients have limited disease involvement, typically defined <5% of body surface area, and can be effectively managed with topical agents such as corticosteroids, vitamin D analogues, tazarotene, etc. For more significant disease, biologics are utilized. Approximately 10-30% of patients with psoriasis will also have PsA. EULAR Recommendations on the management of psoriatic arthritis recommend the following:

- Conventional synthetic DMARDs [(csDMARDs); i.e. MTX, sulfasalazine, leflunomide] should be considered in:
  - Early stage peripheral arthritis, particularly in those with poor prognosis (i.e. swollen joints, structural damage in the presence of inflammation, high erythrocyte sedimentation rate/C reactive protein and/or clinically relevant extra-articular manifestations). MTX is preferred in those with relevant skin involvement
  - After failure to at least one csDMARD, therapy with a bDMARD (usually TNF-i followed by bDMARDs targeting IL-12/23 or IL-17 if TNF-i is not appropriate) should be considered
  - After failure to at least one csDMARD, where a bDMARD is not appropriate, a targeted synthetic DMARD (tsDMARD), such as a PDE4-inhibitor should be considered
  - In those with active enthesitis and/or dactylitis with failure to NSAIDs/local glucocorticoids injections, a bDMARD should be considered (current practice is a TNF-i)
  - Predominantly active axial disease: after failure to NSAIDs, a bDMARD should be considered (current practice is a TNF-i)
  - After failure to a bDMARD, switch to another bDMARD, including switching between TNF-inhibitors

Inflammatory Bowel Disease (IBD)- Crohn’s disease (CD) and Ulcerative Colitis (UC)
American Gastroenterological Association (AGA) 2013 Crohn’s Disease guideline recommendations:

- For Induction of remission in moderately severe CD:
  - Systemic corticosteroids with concomitant thiopurine (6-mercaptopurine or azathioprine) or MTX to help maintain the corticosteroid-induced remission.
  - Anti-TNF (infliximab or adalimumab) with thiopurines are recommended in those refractory to standard therapies (mesalamine, antibiotics, corticosteroids and immunomodulators).
- For Remission in moderately severe CD:
  - Steroid-induced remission: Either 1) thiopurine or MTX OR 2) Anti-TNF with or without thiopurine to maintain remission
- Anti-TNF or Anti-TNF plus thiopurine induced remission: Anti-TNF with or without thiopurine to maintain remission

AGA 2015 Ulcerative Colitis Clinical Care Pathway recommendations: 77
- Patients are to be stratified according to colectomy risk (low vs high)
  - Low risk:
    - Inductive therapy: oral 5ASA and/or rectal 5ASA (first line therapy in distal UC) and/or oral budesonide or prednisone and/or rectal steroids
    - Maintenance therapy: oral 5ASA and/or rectal 5ASA; taper steroid over 60 days
  - High risk, outpatient (3 options):
    - Inductive therapy: short course of steroids with initiation of thiopurine; Maintenance therapy with thiopurine and taper steroids over 60 days OR Anti-TNF ± thiopurine OR vedolizumab ± thiopurine/MTX
    - Inductive therapy: Anti-TNF ± thiopurine; Maintenance with continued anti-TNF ± thiopurine
    - Inductive therapy: vedolizumab ± immunomodulator; Maintenance with continued vedolizumab ± immunomodulator
  - High risk, inpatient (3 options):
    - Induction therapy: IV steroids; Maintenance with thiopurine, anti-TNF ± thiopurine, or vedolizumab ± immunomodulator
    - Induction therapy: infliximab; Maintenance with infliximab ± thiopurine
    - Induction therapy: IV cyclosporine; Maintenance with thiopurine, anti-TNF ± thiopurine, or vedolizumab ± immunomodulator

Ankylosing spondylitis (AS)
2015 ACR/Spondylitis Association of America (SAA)/ Spondyloarthritis Research and Treatment Network (SPARTAN) Recommendations for the treatment of Ankylosing Spondylitis (AS) and Nonradiographic Axial Spondyloarthritis (nr axSpA): 78
- Stable AS: NSAIDs on demand and physical therapy; there is also a conditional recommendation for TNF inhibitor monotherapy
- Active AS: continuous NSAIDs and physical therapy initially and if disease is still active then add a TNF inhibitor (if patient has concomitant inflammatory bowel disease or recurrent iritis, TNF-i monoclonal antibodies, such as infliximab or adalimumab, are recommended over etanercept). If disease activity still continues, despite adding a TNF, switch to a different TNF inhibitor. Glucocorticoids are not recommended, but may be considered in the event of polyarticular flare of peripheral arthritis, IBD flares, or flares during pregnancy.
- Stable nr-axSpA: NSAIDs on demand and physical therapy with TNF inhibitors conditionally recommended
- Active nr-axSpA: same as active AS but it is recommended that steroids not be used under any circumstance

Safety of Biologics
BSR, BHPR- Guidelines on Safety of Anti-TNF Therapies (2010): Although the guideline does not make any recommendation preferring one drug over the other, the following information was provided. 37
- Important differences in the risk of latent TB reactivation exist among the first-generation drugs, with the risk being higher with infliximab and adalimumab than with etanercept, a finding confirmed with recently published data from the French and British biologic registries. Data from the BSRBR have shown that the rate of TB was higher with the monoclonal antibodies adalimumab (144 events/100,000 patient –years [pyrs]) and infliximab (136 events/100,000 pyrs) than with etanercept (39 events/100,000 pyrs). After adjustment, the RR compared with etanercept-treated patients was 3.1 (95% CI 1.0, 9.5) for infliximab and 4.2 (95% CI 1.4, 12.4) for adalimumab. TB has been shown to occur sooner after starting infliximab than etanercept. Forty-three per cent of infliximab associated cases occurred during the first 90 days of treatment, a pattern consistent with reactivation of latent infection. In contrast, etanercept-associated TB cases were distributed evenly throughout the reporting period, with only 10% occurring during the first 90 days of treatment.
References

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