Infliximab may be considered medically necessary as first-line therapy (ie, initial treatment) for the following condition:

Fistulizing Crohn Disease
- reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients with fistulizing Crohn disease⁴;

Infliximab may be considered medically necessary as second-line therapy (ie, for use when first-line therapy fails or is not tolerated) for the following conditions:

Crohn Disease
- reducing signs and symptoms, inducing and maintaining clinical remission in adult and pediatric patients with moderately to severely active Crohn disease who have had an inadequate response to conventional therapy⁵ (ie, sulfasalazine, mesalamine products, corticosteroids, 6-mercaptopurine, azathioprine, cyclosporine, methotrexate);

Ulcerative Colitis
- for reducing signs and symptoms, inducing and maintaining clinical remission and mucosal healing, and eliminating corticosteroid use in patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy⁵ (ie, corticosteroids, azathioprine, 6-mercaptopurine);

Rheumatoid Arthritis
- in combination with methotrexate, reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active
rheumatoid arthritis\(^a\) who have had an inadequate response to one or more disease-modifying antirheumatic drugs (DMARDs; ie, methotrexate, sulfasalazine);

**Ankylosing Spondylitis**
- reducing signs and symptoms in patients with active ankylosing spondylitis\(^a\); in patients who have not had an adequate response to conventional therapy (ie, nonsteroidal anti-inflammatory drugs, sulfasalazine, methotrexate);

**Psoriatic Arthritis**
- reducing signs and symptoms of active arthritis, inhibiting the progression of structural damage, and improving physical function in patients with psoriatic arthritis\(^a\) who have had an inadequate response to one or more DMARDs (ie, methotrexate, sulfasalazine);

**Plaque Psoriasis**
- for the treatment of adults with chronic severe (ie, extensive and/or disabling) plaque psoriasis who are candidates for systemic therapy and when topical therapies, other systemic therapies (ie, methotrexate), and phototherapy are medically less appropriate.\(^a\)

\(^a\) Indication is approved by the U.S. Food and Drug Administration.

Other uses of infliximab are considered investigational, including, but not limited to:
- age-related macular degeneration;
- alcoholic hepatitis;
- arthritis (other than rheumatoid arthritis and psoriatic arthritis);
- Behçet syndrome;
- Behçet syndrome uveitis;
- cancer cachexia;
- depression;
- diabetic macular edema;
- endometriosis;
- erythrodermic or exfoliative psoriasis;
- giant cell arteritis;
- graft-versus-host disease;
- hidradenitis suppurativa
- intra-articular injections;
- juvenile idiopathic arthritis;
- juvenile idiopathic arthritis-associated uveitis;
- Kawasaki disease;
- polyarteritis nodosa;
- polymyalgia rheumatica;
- renal cell carcinoma;
- sacroiliitis;
- sarcoidosis;
- sclerosing cholangitis;
- Sjögren syndrome;
- systemic lupus erythematosus;
• systemic necrotizing vasculitides;
• systemic sclerosis;
• Wegener granulomatosis.

**Cost Effective Disease Modifying Anti-Rheumatic Drugs (DMARD) for Autoimmune Conditions**

There are several brands of DMARD for autoimmune conditions on the market and the following are the most cost effective for Blue Cross of Idaho:

• Remicade (infliximab);
• Orencia (abatacept); and
• Simponi Aria (golimumab).

The cost effective DMARD listed above, may be considered medically necessary when prescribed for the appropriate indication listed in this policy statement above (MP 5.01.15- Infliximab). Only cost effective DMARD may be considered medically necessary, unless the member has a documented contraindication or intolerance to the three cost effective DMARD for autoimmune conditions (i.e., Remicade, Orencia, and Simponi Aria).

Because other DMARD for autoimmune conditions are not as cost effective, they may not be considered a medically necessary alternative; those DMARD not included in the cost effective list include but are not limited to:

• Actemra (tocilizumab);
• Cimzia (certolizumab pegol);
• Entyvio (vedolizumab);
• Inflectra (infliximab-dyyb);
• Renflexis; and
• Stelara (ustekinumab).

**POLICY GUIDELINES**

Infliximab is typically administered initially in a 3-dose induction regimen followed by maintenance therapy every 8 weeks in patients who respond.

**BENEFIT APPLICATION**

**BlueCard/National Account Issues**

State or federal mandates (eg, Federal Employee Program) may dictate that certain U.S. Food and Drug Administration–approved devices, drugs, or biologics may not be considered investigational, and thus these devices may be assessed only by their medical necessity.

Based on benefits or contract language, infliximab may be considered either a pharmacy or a medical benefit.
BACKGROUND

Tumor necrosis factor (TNF) is a cytokine produced by macrophages and T cells. Its name is based on the original observation 25 years ago that TNF killed tumor cells in vitro. Further research has revealed that TNF has a broad spectrum of biologic activities; in particular, it is a key mediator of inflammation and is produced in response to infection and immunologic injury.

There are a number of TNF-α blocking agents: etanercept (Enbrel®; Amgen, Thousand Oaks, CA), adalimumab (Humira®; Abbott, Chicago, IL), and certolizumab pegol (Cimzia®; UCB, Brussels, Belgium) administered via subcutaneous injection; golimumab (Simponi®; Janssen Biotech, Horsham Township, PA) administered subcutaneously or intravenously; and infliximab (Remicade®; Janssen Biotech) administered via an intravenous infusion in the physician's office, outpatient setting, or infusion center. This evidence review focuses on infliximab administered in the physician's office and is thus typically adjudicated under the medical benefit.

Regulatory Status

Initial U.S. Food and Drug Administration (FDA)–labeled indications for infliximab included rheumatoid arthritis and fistulizing Crohn disease (CD), and induction of remission in patients with moderately to severely active CD with an inadequate response to conventional therapy. In 2002, the FDA approved an additional indication for maintenance of clinical remission in CD. Maintenance therapy is designed to prevent disease flares in patients with quiescent disease; drugs most commonly used are azathioprine and 6-mercaptopurine. This new, labeled indication markedly broadened the clinical indications for patients with CD. In December 2004, the FDA approved infliximab for the treatment of ankylosing spondylitis, and, in early 2005, the FDA approved infliximab for the treatment of psoriatic arthritis. In September 2005, the FDA approved infliximab for the treatment of “reducing signs and symptoms, achieving clinical remission and mucosal healing, and eliminating corticosteroid use in patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy.” In May 2006, the FDA approved infliximab for use in pediatric patients with moderately to severely active CD who have had an inadequate response to conventional therapy. In September 2006, the FDA approved infliximab for patients with chronic severe (ie, extensive and/or disabling) plaque psoriasis who are candidates for systemic therapy and when other systemic therapies are medically less appropriate. The need for close monitoring and regular follow-up visits with a physician is noted in FDA approval. In 2011, the FDA approved infliximab for use in pediatric patients ages 6 years and older for the treatment of ulcerative colitis.

Table 1 provides a summary of FDA-approved indications for infliximab and other TNF-α inhibitors (last updated September 2017).

Table 1. FDA-Approved Indications for TNF-α Inhibitors

<table>
<thead>
<tr>
<th>TNF Blocker</th>
<th>Rheumatoid Arthritis</th>
<th>JIA</th>
<th>Crohn Disease</th>
<th>AS</th>
<th>Psoriatic Arthritis</th>
<th>Plaque Psoriasis</th>
<th>Ulcerative Colitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab$^1$</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>· With MTX</td>
<td>Adults and</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>When other</td>
<td>Adults and</td>
</tr>
</tbody>
</table>
### Infliximab

<table>
<thead>
<tr>
<th></th>
<th>After CTF</th>
<th>children ≥6 y, after CTF</th>
<th>systemic therapies are medically less appropriate</th>
<th>children ≥6 y, after CTF</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adalimumab</strong>²</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Alone or with MTX or DMARDs</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Adults and children ≥6 y, after CTF</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Alone or with MTX, ages ≥2 y</td>
<td></td>
</tr>
<tr>
<td><strong>Certolizumab</strong>³</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Adults, after conventional therapy failure</td>
<td></td>
</tr>
<tr>
<td><strong>Etanercept</strong>⁴</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Alone or with MTX</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ages ≥2 y</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>With MTX when response to MTX alone is inadequate</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Adults and children ≥4 y, candidates for systemic</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>therapy or phototherapy</td>
<td></td>
</tr>
<tr>
<td><strong>Golimumab</strong>⁵</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>With MTX</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Alone or with MTX</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>With inadequate response or intolerant to prior</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>treatment or requiring continuous steroid therapy</td>
<td></td>
</tr>
</tbody>
</table>

AS: ankylosing spondylitis; CTF: conventional therapy failure; DMARD: disease-modifying antirheumatic drug; FDA: Food and Drug Administration; JIA: juvenile idiopathic arthritis; MTX: methotrexate; No: agent is not an approved indication; TNF: tumor necrosis factor; Yes: agent is an approved indication.

FDA requires notification to prescribers of risks of invasive fungal infections and monitoring for malignancies with use of TNF blockers. In addition, in March 2013, FDA issued warnings and precautions against concurrent administration of infliximab with other biologic agents. For concurrent administration with other biologic therapeutics, current prescribing information states: “The
concomitant use of Remicade with these biologics is not recommended because of the possibility of an increased risk of infection.”

In April 2016, Inflectra™ (infliximab-dyyb; Celltrion Healthcare) was approved by FDA through the biologics license application process as a biosimilar to Remicade® (Janssen Biotech). In April 2017, Renflexis™ (infliximab-abda; Merck) was approved by FDA through the biologics license application process as a biosimilar to Remicade®. Inflectra™ and Renflexis™ are approved for the same indications as Remicade®, with the exception of pediatric ulcerative colitis.

**RATIONALE**

This evidence review was created in February 2002 and has been updated with searches of the MEDLINE database. The most recent literature update was performed through August 23, 2017. The following is a summary of the key literature to date.

The overall safety of tumor necrosis factor (TNF) inhibitors is discussed briefly, followed by the evidence for the effectiveness of these inhibitors.

Assessment of efficacy for therapeutic intervention involves a determination of whether an intervention improves health outcomes. The optimal study design for this purpose is a randomized controlled trial (RCT) that includes clinically relevant measures of health outcomes. Intermediate outcome measures, also known as surrogate outcome measures, may also be adequate if there is an established link between the intermediate outcome and true health outcomes. Nonrandomized comparative studies and uncontrolled studies can sometimes provide useful information on health outcomes, but are prone to biases such as noncomparability of treatment groups, placebo effect, and variable natural history of the condition.

**TNF Blocker Safety**

Systematic reviews have focused on evaluating the safety of TNF inhibitors. Summaries of the findings are shown in Table 2. TNF inhibitors are associated with several adverse events. In general systematic reviews have shown an increased risk of infections, including herpes zoster, tuberculosis, and opportunistic infections. Regarding increased risk of malignancy, the literature is mixed; many recent meta-analyses have yet to demonstrate an increased risk overall, but some literature has indicated that TNF inhibitor therapy may increase the risk of developing skin cancer(s) and lymphoma. Two systematic reviews have compared safety among TNF inhibitors. One reported no differences in adverse events between TNF inhibitors while the other found higher rates of adverse events and serious infections with infliximab vs adalimumumab or etanercept. Data on long-term safety remain scarce.

**Table 2. Systematic Reviews of Safety of Infliximab and TNF Inhibitors**

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Dates</th>
<th>Studies/N</th>
<th>Population</th>
<th>Design</th>
<th>Summary of Safety Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rungapiromnan et al (2017)</td>
<td>Up to 2016</td>
<td>38/18,024</td>
<td>Psoriasis</td>
<td>RCTs</td>
<td>No increase in risk of major cardiovascular AEs with TNF inhibitors (OR=0.67; 95% CI, 0.10 to 4.63)</td>
</tr>
<tr>
<td>Study</td>
<td>Time Period</td>
<td>Patients</td>
<td>Conditions</td>
<td>Study Type</td>
<td>Findings</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-------------</td>
<td>----------</td>
<td>------------</td>
<td>------------</td>
<td>----------</td>
</tr>
</tbody>
</table>
| Desai et al (2016)³           | Up to 2015  | 61/104,000 | Ankylosing spondylitis, IBD, JAI, plaque psoriasis, psoriatic arthritis, RA | RCTs, OBS | - Risk of treatment discontinuation due to AEs higher with infliximab vs adalimumab or etanercept. Risk for serious infections higher with infliximab vs abatacept, adalimumab, or etanercept.  
- No differences in risk detected for mortality, malignancies, and herpes zoster. |
| Bonovas et al (2016)⁹         | Up to 2016  | 49/14,590 | IBD        | RCTs       | - Biologics associated with increased risk of any infection vs placebo (OR=1.2; 95% CI, 1.1 to 1.3), opportunistic infections (OR=1.9; 95% CI, 1.2 to 3.0), but no serious infections (OR=0.89; 95% CI, 0.7 to 1.1)  
- No increased risk of malignancy (OR=0.90; 95% CI, 0.5 to 1.5) |
| Mocko et al (2016)⁶           | Up to 2016  | 7/4952   | M-to-S ulcerative colitis | RCTs | No difference in AEs, SAEs, or infections between infliximab and other TNF inhibitors |
| Ramiro et al (2014),¹⁰        | Up to 2013  | 49/85,000 | RA         | Cohort, registry | - TNF inhibitors associated with increased risk of serious infections, skin infections (including herpes zoster), and TB reactivation  
- No increase in overall cancer risk but lymphoma and non-melanoma skin cancer risk increased vs general population. Increased risk of melanoma vs other DMARDs |
| EULAR guidelines              |             |          |            |            | |
| Michaud et al (2014),¹¹       | 1990-2013   | 44/11,700 | RA         | RCTs       | - TNF inhibitors associated with increased risk of serious infection (OR=1.4; 95% CI, 1.1 to 1.8), treatment discontinuation due to AEs (OR=1.2; 95% CI, 1.1 to 1.4) vs placebo and/or traditional DMARDs  
- No significantly increased risk of malignancy |
| NIH                           |             |          |            |            | No statistically increased risk of |
| Lopez-Olivo et                | 2000-       | 63/29,423 | RA         | RCTs       | |

**Original Policy Date:** February 2002
### Inflammatory Bowel Disease

In 2017, a systematic review was published on the efficacy and effectiveness of biologics for extraintestinal manifestations of inflammatory bowel disease, such as musculoskeletal, cutaneous, ocular, hematologic, and vascular manifestations. Reviewers included 2 randomized controlled trials (RCTs; n=797), 7 single-arm trials (n=1143), and 13 observational studies (n=914) published before 2010.

<table>
<thead>
<tr>
<th>Study</th>
<th>Year Range</th>
<th>Participants</th>
<th>Condition</th>
<th>Study Type</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moulis et al (2012)</td>
<td>1983-2010</td>
<td>33/7029</td>
<td>RA</td>
<td>RCTs</td>
<td>No statistically increased risk of malignancy vs DMARDs or placebo with up to 2 y of treatment; marginally increased risk of non-melanoma skin cancer with OR=1.9 (95% CI, 1.0 to 3.7)</td>
</tr>
<tr>
<td>Wong et al (2012)</td>
<td>2000-2009</td>
<td>14/7485</td>
<td>RA</td>
<td>RCTs</td>
<td>Increased risk of lymphoma (RD=1.3 lymphomas per 1000 person-years; 95% CI, -0.2 to 2.8; p=0.09)</td>
</tr>
<tr>
<td>Askling et al (2011)</td>
<td>Up to 2010</td>
<td>74/22,904</td>
<td>Any disease condition</td>
<td>RCTs</td>
<td>For anti-TNF vs comparators (RR=1.0; 95% CI, 0.6 to 1.7 for cancers excluding non-melanoma skin cancer; RR=2.0; 95% CI, 1.1 to 4.0 for non-melanoma skin cancer)</td>
</tr>
</tbody>
</table>
| Singh et al (2011)     | Up to 2010 | 209/61,964   | Any disease condition except HIV/AIDS | RCTs, CCTs, OLE | · Higher rate of total AEs for biologics vs controls (OR=1.2; 95% CI, 1.1 to 1.3); increased risk of TB reactivation (OR=4.7; 95% CI, 1.2 to 18.6). Infliximab associated with higher risk of withdrawals due to AEs (OR=2.0; 95% CI, 1.4 to 2.9).  
· No increased rate of SAEs, serious infections, lymphoma, and congestive heart failure |

AE: adverse event; CCT: controlled clinical trial; CI: confidence interval; DMARD: disease-modifying antirheumatic drug; EULAR: European League Against Rheumatism; EMA: European Medicines Agency; NIH: National Institutes of Health; IBD: inflammatory bowel disease; JIA: juvenile idiopathic arthritis; M-to-S: moderate-to-severe; OBS: observational; OLE: open-label extension study; OR: odds ratio; RA: rheumatoid arthritis; RCT: randomized controlled trial; RD: rate difference; RR: relative risk; SAE: serious adverse event; TB: tuberculosis; TNF: tumor necrosis factor.
October 2015. Anti-TNF therapy was associated with improved anemia, arthralgia, arthritis, and ocular manifestations. Infliximab was associated with improved outcomes in bone formation and bone mineral density.

In 2013, Costa et al published a meta-analysis on the rates of hospitalizations and surgeries in patients with inflammatory bowel disease (Crohn disease [CD], ulcerative colitis [UC]) treated with infliximab. Twenty-seven eligible studies (published through May 2012) were included (9 RCTs, 18 observational studies). Overall, 1912 patients were evaluated in these trials (1076 with CD, 836 with UC). Infliximab treatment was associated with a significant odds reduction in hospitalization risk compared with controls, both in RCTs (odds ratio [OR], 0.51; 95% confidence interval [CI], 0.40 to 0.65; $I^2$ test for heterogeneity, 0%) and observational studies (OR=0.29; 95% CI, 0.19 to 0.43; $I^2$=87%). The magnitude of this risk reduction was similar across patients with CD and UC. In patients with CD, RCTs and observational findings on overall major surgery rate were consistent. Infliximab was associated with a significant odds reduction of overall major surgery risk compared with controls, in both RCTs (OR=0.31; 95% CI, 0.15 to 0.64; $I^2$=0%) and observational studies (OR=0.32; 95% CI, 0.21 to 0.49; $I^2$=77%). In patients with UC, pooled results from RCTs and observational studies on overall major surgery rate differed. Infliximab treatment was associated with a significant 43% odds reduction of overall major surgery risk in RCTs (OR=0.57; 95% CI, 0.37 to 0.88; $I^2$=0%), but a nonsignificant increase in pooled results from observational studies (OR=1.43; 95% CI, 0.65 to 3.13; $I^2$=76%). Limitations of this meta-analysis included potential selective reporting and failure to describe withdrawals (attrition bias) in selected RCTs and presentation of unadjusted risk estimates in observational studies. In addition, there was significant heterogeneity in the findings from observational studies, and 3 (17%) of 18 studies were published in abstract form.

In 2012, Lichtenstein et al published a pooled analysis on the safety of long-term infliximab treatment, with or without concomitant immunomodulators, for CD and UC across 10 industry-sponsored studies. These studies included 5 RCTs contributing data from patients who received intravenous (IV) infliximab 5 mg or 10 mg/kg (n=1713; with or without azathioprine) or placebo (n=406; with or without azathioprine). No significant increase in infections, serious infections, or malignancy with infliximab vs placebo was reported in patients with inflammatory bowel disease. For example, when expressed on the basis of incidence per 100 patient-years of follow-up, overlapping 95% CIs indicated that incidences of malignancies were similar in placebo- and infliximab-treated patients who had CD (1.61 [95% CI, 0.19 to 5.82] vs 0.49 [95% CI, 0.18 to 1.06], respectively) or UC (0.00 [95% CI, 0.00 to 1.43] vs 0.60 [95% CI, 0.20 to 1.40], respectively).

**Crohn Disease**

**Systematic Reviews**

Several systematic reviews of RCTs have concluded that TNF inhibitors and specifically infliximab are effective for induction and maintenance of response and remission in the treatment of CD, including moderate-to-severe and fistulizing CD, luminal CD, and CD refractory to conventional treatments. Adverse events reported in clinical trials were similar for infliximab, adalimumab, and certolizumab. In 21 studies enrolling 5356 subjects with CD, anti-TNF therapy did not increase the risk of death, malignancy, or serious infection.
Two network meta-analyses evaluated the comparative efficacy of biologics and immunosuppressants for CD. Hazlewood et al (2015) included 39 RCTs that compared 1 of 6 agents or combined therapy with placebo or another active drug. All agents, including infliximab, were superior to placebo for inducing remission. Adalimumab and combination infliximab plus azathioprine were the most effective regimens at inducing and maintaining remission. Singh et al (2014) included 17 RCTs of good quality in their meta-analyses, and they used Bayesian network analysis to make indirect comparisons. Infliximab was more likely to induce a treatment response than placebo (relative risk [RR], 6.1; 95% CI, 2.5 to 18.3). Infliximab had the highest relative risk for response of the 6 biologic agents (RR range for other agents, 0.61-3.0). Reviewers concluded that infliximab might be the most efficacious agent, but their confidence in this conclusion was low.

Four systematic reviews have examined postoperative complications among CD patients preoperatively treated with infliximab or another anti-TNF therapy vs alternative therapies. In a 2011 systematic review with meta-analysis, Ehteshami-Afshar et al also found an increase in postoperative infections in patients using infliximab for inflammatory bowel disease. Pouch-related complications, sepsis, and thrombotic events also were more common in patients using infliximab. In 2012, Kopylov et al found an increase in postoperative infections associated with preoperative infliximab and “a trend toward an increased risk of noninfectious and overall complications” in comparative cohort studies. In Rosenfeld et al (2013), data were extracted from 6 observational studies published through October 2012 including 1159 patients. The most common complications were wound infections, anastomotic leak, and sepsis. There was no statistically significant difference in major complication rates (OR=1.59; 95% CI, 0.89 to 2.86; p=0.15), minor complication rates (OR=1.80; 95% CI, 0.87 to 3.71; p=0.11), reoperation rates (OR=1.33; 95% CI, 0.55 to 3.20; p=0.52), or 30-day mortality rates (OR=3.74; 95% CI, 0.56 to 25.16; p=0.13) between the infliximab and the control groups. In 2016, Waterland et al compared postoperative abdominal complications in CD patients receiving a preoperative biologic or no therapy. Fourteen retrospective studies (total N=5425 patients) were included. There was an increased risk of total infectious complications associated with anti-TNF therapy (OR=1.52; 95% CI, 1.14 to 2.03) and wound infection (OR=1.73; 95% CI, 1.12 to 2.67). There was no increased risk for other complications including anastomotic leak, abdominal sepsis, or reoperation. A key limitations of these meta-analyses is heterogeneity due to variability in severity, location, and duration of disease, type of surgical procedure, number of surgical procedures included (ie, single or multiple), and surgical method (laparoscopic or open). In addition, most included studies were observational, which can be vulnerable to confounding; and patients receiving infliximab usually have more severe disease and are refractory to other treatments, thereby, possibly being more susceptible to increased complications.

Randomized Controlled Trials

Many RCTs have shown the efficacy of TNF agents and infliximab for treating CD and have been summarized in the systematic reviews discussed above. Trials addressing particular subgroups or clinical questions of interest are described here.

In 2012, Yoshida et al published a prospective, Japanese single-center RCT to assess the efficacy of scheduled maintenance infliximab monotherapy to prevent postoperative CD recurrence. Thirty-one CD patients who had undergone ileocolic resection within the past 4 weeks were randomized to scheduled IV infliximab at 5 mg/kg every 8 weeks for 36 months (n=15) or no infliximab (control arm on conventional medication, if any; n=16). All patients were treated without immunomodulator or
corticosteroid after surgery. Primary and secondary end points were remission rates at 12 and 36 months, defined as Crohn’s Disease Activity Index score of 150 or less, an International Organization for the Study of Inflammatory Bowel Disease score of less than 2, and a C-reactive protein level of less than 0.3 mg/dL. Additionally, endoscopic recurrences at 12 and 36 months were evaluated. At 12 and 36 months, respectively, 100% and 93% of patients in the infliximab group were in remission (International Organization for the Study of Inflammatory Bowel Disease score <2), vs 69% and 56% in the control arm (p<0.03). Similarly, at both time points, 87% of patients in the infliximab group maintained serologic remission (C-reactive protein level <0.3 mg/dL) vs 37.5% in the control arm (p<0.02). Additionally, the infliximab group achieved higher endoscopic remission at 12 months (79% vs 19%; p=0.004). However, in Kaplan-Meier survival analysis, Crohn’s Disease Activity Index scores between the 2 arms did not differ significantly at either 12 or 36 months. No adverse events were observed.

A total of 133 patients were enrolled in a multicenter, open-label RCT in 2008; these patients suffered from active CD not previously treated with corticosteroids, antimetabolites, or biologics, and were assigned to early combined immunosuppression (infliximab plus azathioprine or methotrexate [MTX]) or conventional management (induction with corticosteroids and sequentially adding antimetabolites [azathioprine or MTX] and infliximab) with 2-year follow-up. The results of the RCT revealed that early immunosuppression was more effective than conventional therapy for preventing disease progression. At 26 weeks, 60% vs 36% of the early immunosuppression and conventional treatment groups, respectively, were in remission; remission rates differed statistically at 1 year (62% vs 42%, respectively) but not at 2 years. Corticosteroid, but not antimetabolite, use was lower, and median time to relapse was longer in the early immunosuppression group (329 days vs 175 days). Safety profiles were similar, although the trial was not powered to detect safety differences.

In 2010, the randomized, double-blind SONIC trial was published. In it, 508 adults with moderate-to-severe CD received either infliximab monotherapy, azathioprine monotherapy, or a combination of these 2 drugs. At week 26, corticosteroid-free clinical remission was achieved in 96 (57%) of 169 combination therapy patients, 75 (44%) of 169 infliximab monotherapy patients (p=0.02), and 51 (30%) of 170 azathioprine monotherapy patients (vs combination therapy, p<0.001; vs infliximab, p=0.006). At week 50, numeric trends were similar. Complete mucosal healing at week 26 occurred in 47 (44%) of 107 combination therapy patients, 28 (30%) of 93 infliximab patients (p=0.06), and 18 (17%) of 109 azathioprine patients (vs combination therapy, p<0.001; vs infliximab, p=0.02). In post hoc subgroup analyses, researchers examined the prognostic ability of alternative outcome measures (eg, 50% mucosal healing, C-reactive protein, and Crohn’s Disease Activity Index); none of the outcome measures were shown to predict complete mucosal healing accurately.

In the 2007 REACH trial, 112 children, ages 6 to 17 years, with severe CD (Pediatric Crohn’s Disease Activity Index score >30) who responded inadequately to standard therapy were given IV infliximab therapy. Patients who responded to infliximab therapy at 10 weeks were randomized to 5 mg/kg every 8 or 12 weeks. After 10 weeks of treatment, 99 (88%) of 112 patients responded to infliximab, and 66 (59%) of 112 patients reached clinical remission. After 54 weeks of treatment, clinical remission was achieved in more patients on an 8-week infliximab schedule (29/52 [56%]) than on a 12-week schedule (12/51 [24%]). At 46 weeks, 60 patients continued infliximab treatment for 3 more years in the open-label extension trial. Infliximab was effective in decreasing disease activity to no disease or mild disease in approximately 80% of patients. Serious infection occurred in 10% (6 patients).

**Section Summary: Crohn Disease**
Many systematic reviews and RCTs have established the efficacy of infliximab in patients with inflammatory bowel disease, including moderate-to-severe active CD that is refractory to conventional therapy. Few data are available to directly evaluate the relative efficacy of infliximab and other TNF-blocking agents in the treatment of CD. Indirect comparisons using network meta-analyses have concluded that infliximab, or combination therapy including infliximab, may be the most effective agent for CD, but this conclusion cannot be made with high confidence.

**Ulcerative Colitis**

**Systematic Reviews**

Several systematic reviews with meta-analyses have compared infliximab and cyclosporine as rescue therapies in steroid-refractory UC. In 2016, Narula et al included 3 RCTs and 13 observational studies published through September 2015 (total N=1473 patients). Among the 3 RCTs, there was no significant difference between infliximab and cyclosporine for treatment response and 3- or 12-month colectomy. Among the 13 observational studies (2 prospective, 11 retrospective), infliximab was associated with significantly higher rates of treatment response (OR=2.96; 95% CI, 2.12 to 4.14) and lower 12-month colectomy rate (OR=0.42; 95% CI, 0.22 to 0.83), but not in the 3-month colectomy rate (OR=0.53; 95% CI, 0.22 to 1.28) compared with cyclosporine. There were no significant differences between infliximab and cyclosporine in adverse events, postoperative complications, or mortality.

Komaki et al (2017) compared infliximab, cyclosporine and tacrolimus for the treatment of steroid-refractory, hospitalized UC in a network benefit-risk meta-analysis of 8 RCTs (total N=421 patients) published through November 2015. Five trials were placebo-controlled. The surface under the cumulative ranking identified a rank order of efficacy of infliximab, cyclosporine, tacrolimus, and placebo (see Table 3). The rank order of adverse events leading to discontinuation of therapy was infliximab, tacrolimus, and cyclosporine. Acceptability of treatment (risk-benefit balance) favored infliximab. However, in all analyses of the active treatment the differences were small.

**Table 3. Surface Under the Cumulative Ranking for the Treatment of Ulcerative Colitis**

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Infliximab (95% CI)</th>
<th>Cyclosporine (95% CI)</th>
<th>Tacrolimus (95% CI)</th>
<th>Placebo (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy</td>
<td>0.79 (0.53 to 1.05)</td>
<td>0.77 (0.39 to 1.14)</td>
<td>0.43 (-0.12 to 0.99)</td>
<td>6.67×10⁻³ (6.40×10⁻³ to 0.020)</td>
</tr>
<tr>
<td>Colectomy-free rate</td>
<td>0.74 (0.47 to 1.01)</td>
<td>0.59 (0.17 to 1.01)</td>
<td>0.53 (0.25 to 0.80)</td>
<td>0.13 (-0.033 to 0.29)</td>
</tr>
<tr>
<td>Severe adverse events</td>
<td>0.91 (0.21 to 1.20)</td>
<td>0.33 (-0.24 to 0.90)</td>
<td>0.71 (0.21 to 1.20)</td>
<td>0.040 (0.020 to 0.10)</td>
</tr>
<tr>
<td>Acceptability (risk-benefit)</td>
<td>0.65 (0.37 to 0.92)</td>
<td>0.59 (0.19 to 1.01)</td>
<td>0.53 (0.27 to 0.79)</td>
<td>0.23 (0.033 to 0.42)</td>
</tr>
</tbody>
</table>

CI: confidence interval.

Archer et al (2016) compared infliximab, adalimumab, and golimumab for moderate-to-severe UC that failed conventional therapy in a systematic review and network meta-analysis of 10 RCTs published
before January 2014. The trials suggested that adults receiving infliximab, adalimumab, or golimumab were more likely to achieve clinical response and remission than those receiving placebo. Infliximab was associated with the greatest effect compared with placebo and had the highest probability of being the most effective treatment compared with adalimumab, golimumab, and placebo in the induction phase of treatment (probability of being the best, 0.93). None of the treatments proved to be statistically significantly better than placebo in the maintenance phase from 8 to 32 weeks. Infliximab was most likely to be the most effective treatment among those starting in the state of response at 32 to 52 weeks (probability of being the best, 0.56). Adalimumab was most likely to be the most effective treatment among those starting in remission at 32 to 52 weeks (probability of being the best, 0.84). Hospitalization data were limited but suggested more favorable outcomes for infliximab and adalimumab.

In 2012, Yang et al performed a meta-analysis of observational studies (published through August 2012) to determine the relation between preoperative infliximab use and early postoperative complications in UC patients undergoing abdominal surgery. Thirteen studies involving 2933 patients were included in this meta-analysis. There was no significant association between infliximab therapy preoperatively and total (OR=1.09; 95% CI, 0.87 to 1.37; p=0.47), infectious (OR=1.10; 95% CI, 0.51 to 2.38; p=0.81), or noninfectious (OR=1.10; 95% CI, 0.76 to 1.59; p=0.61) postoperative complications. A significantly decreased risk of infectious complications was reported with infliximab use within 12 weeks before surgery (OR=0.43; 95% CI, 0.22 to 0.83; p=0.01). Publication bias was not observed. However, for the outcome of infectious complications, heterogeneity was significant.

In a 2011 systematic review of treatments for pediatric UC, data from 6 studies on infliximab (total N=126 patients) yielded a pooled short-term response of 75% (95% CI, 67% to 83%) with a 1-year pooled response of 64% (95% CI, 56% to 72%). The U.S. Food and Drug Administration’s (FDA) 2011 approval of infliximab for pediatric use was based on data from a phase 3, randomized, multicenter, open-label study of moderately to severely active UC in patients ages 6 to 17 years. Patients were refractory or unable to tolerate standard therapy with 6-mercaptopurine, azathioprine, corticosteroids, or 5-aminosalicylate. In this study, 44 (73%) of 60 patients responded to infliximab, which was considered to demonstrate efficacy.

**Randomized Controlled Trials**

The FDA’s 2005 approval of infliximab for the treatment of UC was based in part on results of the Active Ulcerative Colitis Trials (ACT) 1 and ACT 2. These RCTs each enrolled 364 patients with disease refractory to at least 1 standard therapy, including corticosteroids, immunosuppressants, or mesalamine. Patients received infliximab or placebo infusions at 0, 2, and 6 weeks and then every 8 weeks thereafter. The ACT 1 trial continued infusions until week 46, with a final evaluation at week 54. In contrast, the ACT 2 trial continued infusions until week 22, with a final evaluation at week 30. The primary endpoint of both trials was the induction of clinical response; secondary end points included clinical remission. In ACT 1, 45% of those in the infliximab 5-mg group, 44% of those in the infliximab 10-mg group, and 20% of those in the placebo group had a clinical response at week 54 (p<0.001 for both vs placebo). In ACT 2, 64% in the infliximab 5-mg group, 69% in the infliximab 10-mg group and 29% in the placebo group had a clinical response at week 8 (p<0.001 for both vs placebo). In both ACT 1 and ACT 2, patients who received infliximab were more likely to have a clinical response at week 30 (p<0.01 for all
Infliximab comparisons). Also, a significantly greater percentage of patients in the infliximab group discontinued steroids during clinical remission. Based on results of these studies, the FDA granted infliximab priority review.

In 2012, Reinisch et al reported on the long-term extension trial of 229 patients from the ACT 1 and ACT 2 trials. The safety profile during the extension trial was consistent with the original trials, and infliximab continued to be effective for up to 3 years. However, infliximab was discontinued in 70 (31%) patients due to adverse events, lack of efficacy, and other reasons.

In 2016, results of CONSTRUCT, a pragmatic, unmasked RCT comparing infliximab and cyclosporine in adults with severe steroid-resistant UC, were reported. CONSTRUCT enrolled 270 participants from 52 hospitals in England, Scotland, and Wales between May 2010 and February 2013. The treatments were IV infliximab 5 mg/kg at 0, 2, and 6 weeks or IV cyclosporine 2 mg/kg/d for 7 days followed by oral cyclosporine 5.5 mg/kg/d for up to 12 weeks. The primary outcome was area under the curve of quality-adjusted survival measured using the Crohn’s and Ulcerative Colitis Questionnaire (CUCQ). The CUCQ was completed at 3 and 6 months, and then every 6 months thereafter. Participants with at least 1 measurement of CUCQ were included (n=242) in the primary intention-to-treat analysis. There was no difference in the area under the CUCQ curve (mean difference, 7.9 favoring cyclosporine; 95% CI, -22.0 to 37.8; p=0.603). Secondary measures of quality of life (EuroQoL 5, 12-Item Short-Form Health Survey) also did not differ between groups. There were no statistically significant differences in colectomy rates, serious adverse events, or concomitant use of immunosuppressants. All 3 deaths that occurred were in the infliximab group.

Section Summary: Ulcerative Colitis

Many systematic reviews and RCTs have established the efficacy of infliximab in patients with inflammatory bowel disease, including acute, steroid-refractory UC. Indirect comparisons from network meta-analyses of RCTs and a direct comparison in a clinical trial have suggested that infliximab and cyclosporin have similar efficacy as second-line treatment for severe UC.

Rheumatoid Arthritis

Rheumatoid arthritis (RA) may be treated with corticosteroids, conventional disease-modifying antirheumatic drugs (DMARDs), and/or TNF inhibitors. DMARDs are a group of medications used in patients with rheumatic diseases that slow the progression of joint damage. Some commonly used conventional synthetic DMARDs are MTX, sulfasalazine, hydroxychloroquine, and leflunomide. MTX is the preferred conventional synthetic DMARD, based on evidence of a substantial clinical benefit and relatively good toxicity profile.

Systematic Reviews

Many systematic reviews have supported the efficacy of TNF inhibitors for patients with RA, particularly as add-on therapy in the second-line setting. One review (2008) suggested a clear benefit of anti-TNF agents over placebo or MTX while another concluded that TNF blockers had comparable outcomes to MTX, but when used in combination, outcomes were superior to those reported with MTX or TNF blockers alone. In 2007, the Canadian Agency for Drugs and Technologies in Health issued a health technology assessment on the long-term clinical effectiveness, safety, and cost-effectiveness of
infliximab and etanercept in rheumatoid arthritis.\textsuperscript{55} Reviewers concluded that infliximab and etanercept used concomitantly with MTX had moderate efficacy in the long-term treatment of active RA resistant to conventional therapy. The short-term (<12 months) safety profile was found acceptable; long-term safety remained a concern.

In 2013, Callhoff et al published a meta-analysis to estimate the impact of biologics on physical function in patients with RA.\textsuperscript{57} Thirty-five RCTs were included in the analysis, 10 with DMARD-naive patients and 25 with DMARD-ineffective or inadequate responders. Of 43 active treatment arms, 5 were with abatacept, 15 with adalimumab, 3 with certolizumab, 7 with etanercept, 4 with golimumab, 5 with infliximab, and 4 with rituximab. Overall, biologic DMARDs led to greater improvements in physical function than nonbiologic DMARDs, with a standardized mean difference in Health Assessment Questionnaire (HAQ) score of 0.44 (95% CI, 0.38 to 0.50). There were no significant differences between individual biologics in both patient groups.

Very few studies have directly compared anti-TNF therapies to one another. Systematic reviews including indirect comparisons have reached conflicting conclusions. Several reviews have found that efficacy appears to be similar among anti-TNF therapies (except anakinra).\textsuperscript{52,53,58,59} However, other reviews have found evidence for the superiority of certain anti-TNF therapies. In a 2012 systematic review, Schmitz et al compared TNF blockers for the treatment of RA using Bayesian mixed treatment comparisons (MTC).\textsuperscript{60} Etanercept and certolizumab were estimated to be more efficacious than infliximab. Additionally, adalimumab, certolizumab, etanercept, and golimumab resulted in better HAQ quality of life outcomes than infliximab. A similar 2011 review by Turkstra et al, using a mixed treatment comparisons approach, suggested that etanercept and certolizumab may be more effective than abatacept, adalimumab, anakinra, golimumab, infliximab, rituximab, or tocilizumab for treatment of RA.\textsuperscript{61} In 2015, Albert conducted an indirect meta-analysis evaluating the comparative efficacy of anti-TNF agents used with a DMARD in DMARD-naive patients.\textsuperscript{62} The biologics performed similarly overall, but etanercept (50 mg) appeared to be superior to infliximab (3 and 6 mg/kg) for one response rate outcome.

In 2012, the Agency for Healthcare Research and Quality (AHRQ) updated its 2007 comparative effectiveness review on RA drug therapy and found that studies did not provide sufficient evidence to determine appropriate strategies for the use of biologic DMARDs, such as infliximab, including when to begin biologic DMARDs and in what drug therapy combinations.\textsuperscript{58} A 2011 systematic review by Malottki et al included adalimumab, etanercept, infliximab, rituximab, and abatacept for treatment of RA after failed treatment with a TNF blocker.\textsuperscript{63} Reviewers concluded that the benefits of using an alternative TNF blocker after a failed first TNF blocker were uncertain. Several studies have addressed dose escalation of infliximab for RA. Two studies by the same research group found better treatment response after increasing infliximab doses up to 10 mg/kg.\textsuperscript{64,65} One of them found no statistically significant differences in the incidence rates of adverse events.\textsuperscript{65} However, Pavelka et al (2009) found that treatment efficacy did not improve and toxicity increased moderately after increasing infliximab dosage to 5 mg/kg.\textsuperscript{66}

Randomized Controlled Trials

A 2014 double-blind RCT in 112 new-onset (duration, 3-12 months), DMARD-naive patients with RA compared the efficacy of MTX and infliximab plus MTX with high-dose IV corticosteroid for remission induction.\textsuperscript{67} At 50-week follow-up, there was no statistical between-group difference in mean modified

\textsuperscript{55} MP 5.01.15

Infliximab
Infliximab

total Sharp score, proportion of patients with radiographic nonprogression, or improvements in quality of life.

In 2012, van Vollenhoven et al reported 2-year results for the randomized, open-label SweFot (Swedish Pharmacotherapy) trial, which compared conventional combination treatment for RA with infliximab therapy in 258 patients refractory to MTX. Clinical treatment response did not differ significantly between groups at 18 and 24 months, and radiographic response did not differ significantly between groups at 18 months. However, the infliximab group had less radiologic disease progression at 24 months (mean, 4.00 vs 7.23; p=0.009). Karlsson et al (2013) examined quality of life outcomes at 21 months and found no statistical between-group difference.

The Abatacept or infliximab vs placebo, a Trial for Tolerability, Efficacy and Safety in Treating rheumatoid arthritis (ATTEST) trial was a head-to-head RCT published by Schiff et al (2008). In this double-blind trial, abatacept and infliximab were compared with placebo in adults with active RA and an inadequate response to MTX. Disease activity decreased more with abatacept (difference in Disease Activity Score, -0.62; 95% CI, -0.96 to -0.29), but remission rates did not differ significantly at 1 year.

Registry Studies

Favalli et al (2016) reported on long-term drug retention rates in a population-based cohort of RA patients who received an anti-TNF therapy as first-line biologic treatment. Data were included from all 583 RA patients treated with a first-line biologic (n=222 infliximab, n=179 etanercept, n=182 adalimumab) between 2003 and 2014 in a single rheumatology unit in Italy. The mean duration of disease was 9 years. Drug retention rate was used to measure overall treatment effectiveness because that rate is affected by drug efficacy, safety, compliance, and alternative treatment options available. The proportions of patients continuing etanercept, adalimumab, and infliximab treatment were 70%, 43%, and 55% after 3 years; 65%, 37%, and 44% after 5 years; and 53%, 20%, and 17% after 12 years, respectively. The propensity score–adjusted hazard ratio (HR) for treatment discontinuation was significantly greater for infliximab than etanercept (HR=2.56; 95% CI, 1.92 to 3.4). Etanercept showed a lower frequency of discontinuation than infliximab, which was attributed to inefficacy (17.5% and 44.1%; p<0.001) and adverse events (22.4% and 36.7%; p<0.001), both respectively.

Section Summary: Rheumatoid Arthritis

The evidence for infliximab in patients who have RA includes RCTs and systematic reviews of RCTs. Many RCTs have reported improvements in symptoms, disease remission, functional status, and quality of life associated with infliximab treatment particularly when used as add-on therapy in the second-line setting. A limited number of head-to-head comparative trials have evaluated the relative efficacy of infliximab and other TNF-blocking agents in the treatment of RA. Available trials and indirect comparisons have suggested that infliximab is roughly equivalent to other TNF-α medications, although some indirect and registry evidence has suggested that etanercept might be superior to infliximab.

Ankylosing Spondylitis

Several systematic reviews have confirmed that TNF-α inhibitors reduce disease activity and improve functional capacity compared with placebo in patients with either ankylosing spondylitis or nonradiographic axial spondyloarthritis.
In 2016, the National Institute for Health Research published a health technology assessment on TNF-α inhibitors for ankylosing spondylitis. Twenty-eight RCTs of adalimumab, certolizumab pegol, etanercept, golimumab, or infliximab for the treatment of severe active ankylosing spondylitis or severe nonradiographic axial spondyloarthritis published before July 2014 were included. Effectiveness data from RCTs were synthesized using Bayesian network meta-analysis methods. The short- and long-term clinical effectiveness of TNF-α inhibitors was found to be similar across TNF-α inhibitors, although data on long-term outcomes were limited. There was little evidence on the impact of TNF-α inhibitors on delaying disease progression. Infliximab is associated with significantly higher rates of total adverse events and withdrawals because of adverse events.

A 2015 Cochrane Collaboration review on TNF-α inhibitors for ankylosing spondylitis included 21 trials of different TNF-α inhibitors. Three RCTs compared infliximab with placebo and 1 trial compared infliximab with etanercept. Most trials allowed concomitant use of other DMARDs, steroids, and/or nonsteroidal anti-inflammatory drugs (NSAIDs). The likelihood of achieving a response, as defined by Assessment of SpondyloArthritis international Society–40 (ASAS 40) criteria, was greater for infliximab than for MTX alone (RR=4.07; 95% CI, 2.80 to 5.74). There was also high-quality evidence that infliximab is associated with a clinically significant improvement in physical functioning. The evidence on the comparative efficacy of infliximab with other agents was inconclusive.

Section Summary: Ankylosing Spondylitis

The evidence for infliximab in patients who have ankylosing spondylitis includes RCTs and systematic reviews of RCTs. Summaries from systematic reviews have reported improvements in response rates and physical functioning with infliximab treatment. There is a lack of head-to-head comparative trials evaluating the relative efficacy of infliximab and other TNF-blocking agents in the treatment of ankylosing spondylitis. Indirect evidence from network meta-analysis has suggested TNF-blocking agents have similar effectiveness.

Plaque Psoriasis and Psoriatic Arthritis

Systematic Reviews

The effectiveness of infliximab and other TNF inhibitors compared with placebo for treating moderate-to-severe psoriasis has been shown in systematic reviews of RCTs. Nast et al (2015) pooled results from 25 RCTs of long-term treatments for moderate-to-severe psoriasis and showed that, with respect to response measured by the Psoriasis Area and Severity Index (PASI), infliximab was superior to placebo in long-term therapy (RR=13.07; 95% CI, 8.60 to 19.87).

In 2012, AHRQ updated its 2007 report on drug therapy for adult psoriatic arthritis. Reviewers found that evidence on biologic DMARDs was limited, although symptom improvement had been reported. Reviewers noted that firm conclusions could not be drawn about the comparative efficacy, effectiveness, functional status, health-related quality of life, or tolerability of DMARDs, including infliximab. Several systematic reviews assessed the comparative effectiveness and safety of TNF inhibitors for psoriasis and psoriatic arthritis and reported no significant differences in effectiveness and overall adverse reactions between available anti-TNF agents. However, other systematic reviews have found evidence of superiority of select TNF inhibitors. In 2011, a systematic review, with network
meta-analysis, of infliximab, etanercept, and adalimumab for psoriasis, concluded that each of these agents was effective in reducing skin disease and joint symptoms, but infliximab was more effective in improving skin and joint outcomes compared with etanercept and adalimumab. Migliore et al (2012) conducted a mixed treatment comparison analysis of etanercept, infliximab, and adalimumab and found that American College of Rheumatology 20 (ACR 20) scale response occurred more commonly with etanercept than with placebo. Reich et al (2012) compared biologics available in Europe for the treatment of moderate-to-severe psoriasis in adults using network meta-analysis. The highest predicted mean probability of response occurred with infliximab at PASI response level of 50 (93%), 75 (80%), and 90 (54%), followed by ustekinumab 90 mg, ustekinumab 45 mg, adalimumab, etanercept, and efalizumab. In another 2012 systematic review and meta-analysis, Lucka et al found that infliximab and ustekinumab were most effective over 24 weeks followed by adalimumab and etanercept. The effectiveness of infliximab, adalimumab, and etanercept decreased after 24 weeks. Using a network meta-analysis to make indirect comparisons, Ungprasert et al (2016) found that, among patients who had persistently active disease despite NSAIDs, DMARDs, or who could not tolerate NSAIDs and DMARDs, those who received etanercept, infliximab, adalimumab, and golimumab had a statistically significantly higher chance of achieving response measured by the ACR 20 scale compared with apremilast, ustekinumab, and certolizumab.

In 2012, AHRQ published a comparative effectiveness review on the benefits and harms of anti-TNF or biologic systemic agents compared with nonbiologic systemic agents or phototherapy in patients with chronic plaque psoriasis. In total, 5 RCTs (n=1227 patients) and 4 observational studies (n=1066 patients) published through June 2012 were selected. These studies directly compared a systemic biologic agent with a systemic nonbiologic agent or phototherapy and reported at least one outcome of interest. Five RCTs (two good, two fair, one poor-quality) and two fair-quality observational studies evaluated the comparative effectiveness of systemic biologic agents and systemic nonbiologic agents. The comparisons included adalimumab, etanercept, infliximab, and ustekinumab vs MTX, and etanercept vs acitretin. Comparative effectiveness of these therapies with regard to final health outcomes other than health-related quality of life could not be determined due to a lack of evaluation in the selected literature. Compared with MTX, health-related quality of life improved in patients taking infliximab, based on a single RCT (low strength of evidence). There was insufficient evidence to evaluate major organ system toxicities due to anti-TNF therapy, and no other final health outcomes were reported. Evidence for the comparative safety of systemic biologic agents and systemic nonbiologic agents or phototherapy was sparse. Overall, there were no studies that directly compared infliximab with other biologics/agents in the evaluation of harms.

Randomized Controlled Trials

The 2005 Infliximab Multinational Psoriatic Arthritis Controlled Trial (IMPACT) was a randomized, placebo-controlled, blinded study of infliximab for the treatment of psoriatic arthritis. A secondary outcome focused on improvements in dermatologic manifestations of psoriasis. Of 104 participants, only 39 (38%) had significant psoriatic skin lesions, as evidenced by a PASI score of 2.5 or greater. (Maximum PASI score is 72 [lesional erythema, scaling, and thickness in 4 anatomic areas].) Patients received infliximab or placebo at 0, 2, 6, and 14 weeks. After week 16, patients initially assigned to receive placebo crossed over to receive infliximab every 8 weeks through week 50, and patients randomized to infliximab continued to receive active treatment. Changes in PASI score were analyzed for the 39 patients with skin lesions; 68% of infliximab patients achieved a PASI response of 75% or more at week 16 compared with none in the placebo group. However, interpretation of these results was
limited by small sample size. Additionally, patients were recruited to this trial based on arthritic manifestations with previous failure of one or more DMARD; it is unknown whether previous therapies had been successful in controlling dermatologic manifestations of psoriasis.

Gottlieb et al (2004) reported on a larger trial of 249 patients with severe plaque psoriasis who were randomized to receive an infusion of 1 of 2 different doses of infliximab or placebo at 0, 2, and 6 weeks. In contrast to the IMPACT study, which enrolled patients with a PASI score of 2.5 or greater, this study enrolled patients with a PASI score of 12 or greater and with psoriatic plaques covering at least 10% of body surface area. The primary end point was the proportion of patients who achieved a PASI response of at least 75% improvement from baseline at week 10. At week 10, 72% of patients treated with infliximab 3 mg/kg and 88% of patients treated with infliximab 5 mg/kg achieved a PASI response of 75% or greater improvement from baseline, compared with 6% in the placebo group (p<0.001 for both comparisons vs placebo). Although no study directly compared various agents, these positive results were considered similar to those associated with cyclosporine, better than those associated with etanercept, and better than topical agents. Results from this larger trial demonstrated the efficacy of infliximab in patients with moderately severe psoriasis who met study criteria.

In 2010, Atteno et al reported on a randomized trial of 100 patients treated with infliximab, etanercept, or adalimumab for psoriatic arthritis. All 3 agents effectively controlled signs and symptoms of psoriatic arthritis at 12 months.

In 2012, Baranauskaite et al reported on the randomized, open-label RESPOND trial, which compared infliximab plus MTX with infliximab alone in 115 patients with psoriatic arthritis. Infliximab plus MTX yielded greater improvements in outcomes and disease suppression than MTX alone. In an intention-to-treat analysis at 16 weeks, 44 (86%) of 51 patients in the infliximab plus MTX group achieved an ACR 20 response vs 32 (67%) of 48 patients in the MTX-only group (p=0.021). ACR 50 and ACR 70 responses were also significantly greater in the combination treatment group. Improvements in PASI scores were statistically significantly greater in the combination treatment group at each time point; mean reduction in PASI score by 16 weeks was 93.3% in the combination group and 67.4% in the MTX-only group (p=0.003). Although adverse events were higher in the combination group, most were considered to be mild to moderate. Barker et al (2011) reported on a randomized, open-label study of infliximab vs MTX in 868 MTX-naive patients with moderate-to-severe plaque psoriasis in the RESTORE1 trial. At 16 weeks, significantly more patients achieved PASI 75 response in the infliximab-treated group (508/653 [78%]) than in the MTX group (90/215 [42%]; p<0.001).

Results from the Psoriasis Infliximab versus Etanercept Comparison Evaluation (PIECE) trial were published in 2017. PIECE is a multicenter RCT comparing etanercept 50 mg subcutaneous twice-weekly (n=23) with infliximab 5 mg/kg (at weeks 0, 4, 6, 14, and 22) (n=25) in adults with moderate-to-severe chronic plaque psoriasis who had failed or could not tolerate ultraviolet therapy, MTX, or cyclosporine. Patients were not blinded, but efficacy outcome assessment was performed by blinded assessors. At 24 weeks, 72% in the infliximab group and 35% in the etanercept group had a PASI 75% response or greater improvement (p<0.001). Mean Skindex-17 Symptoms score was significantly lower in the infliximab group at week 12 (3.9 vs 2.4, respectively; p=0.02). Mild adverse events were reported in 76.1% of infliximab patients vs 66.2% of etanercept patients.

**Section Summary: Plaque Psoriasis and Psoriatic Arthritis**
The evidence for infliximab in patients who have plaque psoriasis or psoriatic arthritis includes RCTs and systematic reviews of RCTs. A few RCTs have reported improvements in symptoms and quality of life for infliximab compared with placebo. We lack head-to-head comparative trials evaluating the relative efficacy of infliximab and other TNF-blocking agents in the treatment of psoriasis; a small RCT has compared infliximab with etanercept.

**Juvenile Idiopathic Arthritis**

In 2011, AHRQ published a comparative effectiveness review of DMARDs for children with juvenile idiopathic arthritis (JIA). Reviewers found that evidence on biologic DMARDs was limited, although symptom improvement had been reported. Heterogeneity of studies and in outcome reporting, as well as varied categories of JIA, made meaningful comparisons of DMARDs difficult. Additionally, many questions remained regarding the safety of DMARDs in children, especially because of the associated malignancy risk, particularly for lymphoma, with the use of TNF-α blocking agents.

Ruperto et al (2010) reported on an open-label extension trial of infliximab for JIA in 78 children. However, this study was limited by the high number of patients who discontinued infliximab treatment (42 [58%] patients) for various reasons. Of the remaining 36 patients, 40% achieved American College of Rheumatology Pediatric (ACR-Pedi) 50 response criteria at week 204, whereas 33% achieved ACR-Pedi 70 during this time period. Thirteen percent of patients achieved inactive disease status.

In a 2011 report of a multicenter, 54-week, randomized, open-label trial of JIA (N=60) by Tynjala et al, patients taking infliximab plus MTX had better outcomes than those taking MTX alone or in combination with sulfasalazine and hydroxychloroquine. In patients taking infliximab, all 19 achieved ACR-Pedi 75 compared with 13 (65%) of 20 on combination treatment and 10 (50%) of 20 on MTX. Thirteen (68%) of patients taking infliximab achieved inactive disease status compared with 8 (40%) and 5 (25%) in the combination and MTX groups, respectively. Inactive disease also continued for a longer duration in the infliximab group (mean, 26 weeks) than in the combination and MTX groups (mean, 13 weeks and 6 weeks). A 2010 evidence-based review noted that infliximab is frequently used to treat JIA in clinical practice, despite not having FDA approval for this indication.

**Section Summary: Juvenile Idiopathic Arthritis**

The evidence for infliximab in patients who have JIA includes an RCT with 60 children and uncontrolled studies. Larger trials are needed to confirm efficacy. Very few data are available on the safety of TNF inhibitors in children.

**Off-Label infliximab for other rheumatic or muculoskeletal conditions**

In addition to its labeled uses, infliximab is being studied in treatment-refractory inflammatory diseases and other varied indications. The discussion here only includes RCTs and systematic reviews reporting the use of infliximab or other TNF-α blocking agents.

**Sarcoidosis**
Analyzes from a previously published randomized trial of 138 patients with pulmonary sarcoidosis were reported in 2008.\textsuperscript{100,101} Patients received infliximab or placebo for 24 weeks. An outcome metric designed for the study, the Physician Organ Severity Tool, summarized the involvement of 17 extrapulmonary organs. Although a statistical improvement in group mean score was noted at 24 weeks with infliximab, the outcome metric had not been clinically validated, and its relation to clinical outcomes was unknown. In a 2011 publication from the same authors, levels of inflammatory serum proteins were reduced in 134 sarcoidosis patients who received infliximab in the original trial.\textsuperscript{102} Maneiro et al (2012) conducted a systematic review of sarcoidosis treatment with TNF blockers.\textsuperscript{103} Reviewers found insufficient evidence to support the use of TNF blockers for the treatment of sarcoidosis.

**Scleroderma (Systemic Sclerosis)**

A 2011 systematic review evaluated 3 observational studies on biologics for systemic sclerosis.\textsuperscript{104} Infliximab and etanercept treatment resulted in improved inflammatory arthritis and disability scores on the disability index of the Health Assessment Questionnaire. Reviewers noted the need for larger, long-term studies to understand the role of biologics for the treatment of scleroderma.

**Sjögren Syndrome**

A 2010 systematic review found anti-TNF agents have not demonstrated effectiveness in the treatment of Sjögren syndrome.\textsuperscript{105} Included in the review were 2 placebo-controlled trials of infliximab and etanercept, and 2 trials of fewer than 30 patients. In placebo-controlled trials, anti-TNF agents did not improve joint pain, fatigue, or dryness, as measured by a composite visual analog scale, and reviewers concluded these agents were not clinically effective.

**Uveitis**

In 2014, Simonini et al published 2 systematic reviews with meta-analyses of anti-TNF agents for treatment of autoimmune chronic uveitis in refractory pediatric (≤16 years old) patients.\textsuperscript{106,107} In both studies, the primary outcome was the change in intraocular inflammation using standardized criteria validated in adults but not in children. One study included only patients previously untreated with biologic agents.\textsuperscript{106} The literature was searched through September 2012; 23 studies (1 RCT of etanercept and 22 retrospective studies; total N=229 patients) were included. Most patients (63%) received infliximab; 24% received etanercept; and 13% received adalimumab. A meta-analysis of observational studies showed high response rates with infliximab (72%; 95% CI, 64% to 79%) and adalimumab (87%; 95% CI, 75% to 98%; vs infliximab, p=0.08) but not with etanercept (33%; 95% CI, 19% to 47%; vs either group, p<0.001). The other study examined changing anti-TNF following the failure of an initial anti-TNF course.\textsuperscript{107} Literature was searched through April 2013; 10 observational studies were included (total N=40 patients). Ninety-eight percent of patients had JIA, the leading cause of autoimmune chronic uveitis in children. Most children (58%) were switched from infliximab to adalimumab; 27% were switched from etanercept to adalimumab; and 15% were switched from etanercept to infliximab. Thirty (75%) patients responded to treatment, 6 (100%) of 6 children on infliximab and 24 (32%) of 34 children on adalimumab. Adverse events occurred in 6 (23%) of 26 children; 5 taking adalimumab reported local pain or discomfort, and 1 taking infliximab reported transient bronchospastic cough. Adverse event severity was not reported. Although results suggested that switching between anti-TNF drugs may be
appropriate in some patients when the response to a first anti-TNF drug is insufficient, the conduction of further RCTs are still recommended.

In 2013, Cordero-Coma et al published a systematic review of anti-TNF agents for managing uveitis.\textsuperscript{108} A total of 54 studies (published through October 2011) were included. Evidence for infliximab comprised 4 open trials, 1 cross-sectional study, 12 prospective studies, and 33 retrospective studies and/or case series (total N=517 patients). Reviewers rated the level of evidence for infliximab for the treatment of noninfectious immune-mediated uveitis as level 2b (findings based on extrapolation from individual cohort study, or low-quality RCTs). Selected studies had several limitations, including poor study designs, heterogeneity of the study variables, lack of standardized methods to assess treatment efficacy for uveitis, and variable treatment outcome measures.

**Hidradenitis Suppurativa**

A Cochrane review of interventions for hidradenitis suppurativa was published in 2016.\textsuperscript{109} Twelve trials with 15 interventions published between 1983 and 2015 were included. One RCT of infliximab was selected; 38 participants were enrolled and 33 completed follow-up.\textsuperscript{110} Infliximab improved the Dermatology Life Quality Index score relative to placebo (difference in mean change, 1.61; 95% CI, 0.64 to 3.86) at 8 weeks. A 50% increase in serious adverse events was reported in the infliximab group (RR=1.47; 95% CI, 0.26 to 8.44). The trial was rated as of moderate quality.

Two 2013 systematic reviews evaluated anti-TNF agents in hidradenitis suppurativa; based on data from observational studies, moderate-to-good response rates were observed in over 80% of patients treated with infliximab.\textsuperscript{111,112} However, evidence quality was low overall and differed among the agents, making direct comparisons difficult. Two 2012 systematic reviews have also suggested a role for infliximab in the treatment of hidradenitis suppurativa.\textsuperscript{113,114} A retrospective study of 19 patients treated at 7 tertiary care centers in Spain was published in 2015.\textsuperscript{115} Approximately 40% of patients received infliximab as initial therapy and approximately 60% received adalimumab; 50% of patients eventually received a second biologic agent. Three (16%) patients had a complete response, 10 (53%) had a partial response, and 6 (32%) had no response.

**Behçet Disease**

A 2011 evidence-based review suggested that there may be a role for biologics in the treatment of Behçet disease.\textsuperscript{116} A single-arm prospective study performed at 21 institutions in Japan was published in 2016.\textsuperscript{117} Eighteen participants diagnosed with complete or incomplete Behçet disease, neurologic Behçet, or vascular Behçet disease were enrolled. They received IV infliximab 5 mg/kg at weeks 0, 2, and 6, and every 8 weeks thereafter until week 46. Eleven (61%) of the 18 were complete responders at weeks 14 and 30. Scarring or healing of the principal ulcer was observed in 80% of the participants. Infections occurred in 11 participants. Further study and the implementation of additional RCTs are needed.

**Vasculitides**

Preliminary studies have investigated infliximab for treatment of Wegener granulomatosis\textsuperscript{118} and other vasculitides. A 2007 placebo-controlled trial of 44 patients with giant cell arteritis was terminated early due to lack of treatment effect for clinical outcomes at interim analysis.\textsuperscript{119} In subsequent analysis, serum
Infliximab inflammatory biomarkers and markers of vascular remodeling on temporal artery biopsy did not differ between groups.\textsuperscript{120}

Silva-Fernandez et al (2014) conducted a systematic review of biologic therapies for systemic vasculitides.\textsuperscript{121} Literature was searched through April 2013; of 80 selected studies, 29 primarily uncontrolled, observational studies assessed TNF inhibitors (infliximab, etanercept, adalimumab, golimumab). Evidence was contradictory for infliximab efficacy in antineutrophil cytoplasmic antibody-associated vasculitides (granulomatosis with polyangiitis and microscopic polyangiitis, an eosinophilic granulomatosis with polyangiitis) and in large vessel vasculitides (giant cell arteritis, Takayasu arteritis).

Kawasaki Disease

Preliminary studies have investigated infliximab for the treatment of refractory Kawasaki disease.\textsuperscript{122,123} Tremoulet et al (2014) conducted a phase 3, double-blind RCT in 196 children (age, 4 weeks to 17 years) with active (fever ≥38°C) Kawasaki disease.\textsuperscript{124} Patients were randomized 1:1 to a single dose of infliximab or placebo administered before IV immunoglobulin therapy. There was no statistical between-group difference in the primary outcome (immunoglobulin resistance) defined as return or persistence of fever (11% both groups, p=0.81). The observed reductions (noted at week 2) in fever duration, serum inflammatory markers, and left anterior descending coronary artery dimension did not persist to week 5.

Renal Cell Carcinoma

Two phase 2 trials of infliximab as a treatment for refractory renal cell carcinoma (n=18 treated with 10 mg/kg, n=19 treated with 5 mg/kg) showed partial response or stable disease, with 61% of those receiving the higher dose; the results of these trials revealed that the disease stabilized over a median duration of 7.7 months.\textsuperscript{125} One death due to infection was reported as well.

Pain Syndromes

Infliximab and other TNF inhibitors have been investigated for the treatment of various pain syndromes. Two systematic reviews of low back pain with radiculopathy (sciatica) found insufficient evidence to conclude that TNF inhibitors were safe or effective for treatment of these conditions.\textsuperscript{126,127} A placebo-controlled randomized trial (2013) of 13 patients with complex regional pain syndrome found statistically significant reductions in quality of life in patients who received infliximab.\textsuperscript{128} Preliminary studies have investigated infliximab for treatment of sacroiliitis\textsuperscript{129} and endometriosis-associated pelvic pain.\textsuperscript{130,131}

Mixed Indications

Preliminary studies have investigated infliximab for treatment of pemphigus vulgaris,\textsuperscript{132} severe alcoholic hepatitis,\textsuperscript{133} systemic lupus erythematosus,\textsuperscript{134} and diabetic macular edema.\textsuperscript{135} A number of placebo-controlled trials of infliximab were conducted for other indications such as polymyalgia rheumatica (N=51), sclerosing cholangitis (N=24), non-small-cell lung cancer–related weight loss (N=61), depression, graft-versus-host disease, depression (N=89).\textsuperscript{136-142} None of these trials showed a clinical benefit of infliximab for their stated outcomes. Although small sample sizes may account for
some lack of reported effect due to reduced power, a study of sclerosing cholangitis was terminated early due to lack of treatment effect at interim analysis.\textsuperscript{138} Other studies have also reported negative results. Infliximab was not effective for the treatment of age-related macular degeneration in an open-label, randomized, single-center phase 1/2 pilot study.\textsuperscript{143} Intra-articular injections of infliximab were not effective in treating chronic or recurrent gonarthritis in a randomized crossover study (2009) of 23 patients (41 total intra-articular injections: 20 infliximab and 21 methylprednisolone).\textsuperscript{144} In this study, improvements were greater with methylprednisolone.

Placebo-controlled studies reporting minimal or no benefit of infliximab treatment in a variety of inflammatory diseases for which epidemiologic evidence had suggested benefit are sobering, given the drug’s toxicities. Well-designed, comparative studies are still needed.

**Section Summary: Other Rheumatic or Musculoskeletal Conditions**

The evidence on off-label infliximab for individuals who have other rheumatic or musculoskeletal conditions potentially treatable with TNF-\(\alpha\) inhibitors includes systematic reviews, a smaller number of RCTs, and a large number of uncontrolled studies. For most conditions, there are no RCTs to determine treatment efficacy and few comparative prospective studies. For some conditions (eg, sarcoidosis, Sjögren syndrome), a few small RCTs have not reported benefit.

**Summary of Evidence**

For individuals who have Crohn disease who receive infliximab, the evidence includes RCTs and systematic reviews of RCTs. Relevant outcomes are symptoms, change in disease status, health status measures, quality of life, and treatment-related morbidity. These trials have demonstrated that infliximab has efficacy in inducing remission, maintaining remission, reducing the formation of fistulas, and preventing recurrence postoperatively. A limited number of head-to-head comparative trials have evaluated the relative efficacy of infliximab and other TNF-blocking agents in the treatment of Crohn disease. Indirect comparisons using network meta-analysis have concluded that infliximab, or a combination therapy including infliximab, may be the most effective agent; however, this conclusion cannot be made with high confidence. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have ulcerative colitis who receive infliximab, the evidence includes RCTs and systematic reviews of RCTs. Relevant outcomes are symptoms, change in disease status, health status measures, quality of life, and treatment-related morbidity. The available trials have demonstrated that infliximab has efficacy in inducing remission and decreasing the dose of steroids; further, a network meta-analysis of RCTs found that infliximab is effective and has an acceptable risk-benefit profile as second-line therapy compared with cyclosporine and tacrolimus. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have rheumatoid arthritis who receive infliximab, the evidence includes RCTs and systematic reviews of RCTs. Relevant outcomes are symptoms, change in disease status, health status measures, quality of life, and treatment-related morbidity. Many RCTs have reported improvements in symptoms, disease remission, functional status, and quality of life associated with infliximab treatment. A limited number of head-to-head comparative trials have evaluated the relative efficacy of infliximab and other TNF-blocking agents in the treatment of rheumatoid arthritis. Available trials and indirect
comparisons have suggested that infliximab is roughly equivalent to other TNF-α medications. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have ankylosing spondylitis who receive infliximab, the evidence includes RCTs and systematic reviews of RCTs. Relevant outcomes are symptoms, change in disease status, health status measures, quality of life, and treatment-related morbidity. A few RCTs have reported improvements in response rates and physical functioning with infliximab treatment. It should be noted, however, that there remains a lack of head-to-head comparative trials evaluating the relative efficacy of infliximab and other TNF-blocking agents in the treatment of ankylosing spondylitis. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have plaque psoriasis or psoriatic arthritis who receive infliximab, the evidence includes RCTs and systematic reviews of RCTs. Relevant outcomes are symptoms, change in disease status, health status measures, quality of life, and treatment-related morbidity. A few RCTs have reported improvement in symptoms and quality of life. Again, there is a lack of head-to-head comparative trials evaluating the relative efficacy of infliximab and other TNF-blocking agents in the treatment of psoriasis. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have juvenile idiopathic arthritis who receive infliximab, the evidence includes a small RCT and uncontrolled studies. Relevant outcomes are symptoms, change in disease status, health status measures, quality of life, and treatment-related morbidity. Larger trials are needed to confirm efficacy. Very few data are available on the safety of TNF inhibitors in children. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have rheumatic or musculoskeletal conditions potentially treatable with TNF-α inhibitors who receive infliximab off-label, the evidence includes a smaller number of RCTs and a large number of uncontrolled studies. Relevant outcomes are symptoms, change in disease status, health status measures, quality of life, and treatment-related morbidity. For most conditions, there is a lack of RCTs to determine treatment efficacy. For some conditions (eg, sarcoidosis, Sjögren syndrome), there are a few small RCTs that have not reported benefit. The evidence is insufficient to determine the effects of the technology on health outcomes.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

Crohn Disease

American Gastroenterological Association Institute

In 2013, the American Gastroenterological Association Institute published guidelines on the use of thiopurines, methotrexate, and anti-tumor necrosis factor (TNF)-α biologic drugs for induction and maintenance of remission in inflammatory Crohn disease. The following recommendations were developed using the GRADE methodology (see Table 4).
Table 4. Recommendations for Induction and Maintenance Therapy for Inflammatory Crohn Disease

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>SOR</th>
<th>QOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use anti-TNF-α drugs to induce remission in patients with moderately severe CD</td>
<td>Strong</td>
<td>Moderate</td>
</tr>
<tr>
<td>Use anti-TNF-α monotherapy over thiopurine monotherapy to induce remission in patients with moderately severe CD</td>
<td>Strong</td>
<td>Moderate</td>
</tr>
<tr>
<td>Use anti-TNF-α drugs with thiopurines over anti-TNF-α monotherapy to induce remission in patients with moderately severe CD</td>
<td>Weak</td>
<td>Moderate</td>
</tr>
<tr>
<td>Use anti-TNF-α drugs over no anti-TNF-α drugs to maintain corticosteroid or anti-TNF-α-induced remission in patients with CD</td>
<td>Strong</td>
<td>High</td>
</tr>
</tbody>
</table>


In 2017, the Association Institute provided a conditional recommendation, based on moderate quality of evidence, to initiate or optimize anti-TNF and/or thiopurine therapy over continued monitoring alone following surgically induced remission of Crohn disease.\(^{147}\)

**Rheumatoid Arthritis**

**American College of Rheumatology**

In 2015, the American College of Rheumatology (ACR) published a guideline on the treatment of rheumatoid arthritis.\(^{148}\)

- In patients with early rheumatoid arthritis (disease duration, <6 months), anti-tumor necrosis factor (TNF) biologics with or without methotrexate are recommended for patients who have high disease activity with poor prognostic features (functional limitation, extra-articular disease, positive rheumatoid factor, positive anti-cyclic citrullinated peptide antibodies, bony erosions by radiograph) despite disease-modifying antirheumatic drug (DMARD) monotherapy. The level of evidence was determined to be low; data derived from multiple randomized controlled trials, a single randomized trial, or nonrandomized studies. Infliximab is an exception and is recommended for use in combination with methotrexate but not as monotherapy.
- For patients with established rheumatoid arthritis (disease duration, ≥6 months), biologic agents, including anti-TNF drugs, are recommended if disease activity is moderate or high after 3 months of methotrexate therapy alone or in combination with other conventional DMARDs. The level of evidence was determined to be moderate-to-very low; data were derived from multiple randomized controlled trials, a single randomized trial, nonrandomized studies, consensus opinion, case studies, or standards of care.

**National Institute for Health and Care Excellence**

The National Institute for Health and Care Excellence’s 2010 guidance on rheumatoid arthritis recommended TNF-α inhibitors, including infliximab, for adults who cannot tolerate or have failed other disease-modifying drugs.\(^ {149}\)

**Ankylosing Spondylitis**
In 2015, ACR and the Spondylitis Association of America and the Spondyloarthritis Research and Treatment Network published recommendations for treatment of ankylosing spondylitis and nonradiographic axial spondyloarthritis (see Table 5).  

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>In adults with active ankylosing spondylitis (AS) despite treatment with nonsteroidal anti-inflammatory drugs (NSAIDs), treatment with TNF inhibitors are strongly recommended. No particular TNF inhibitor is recommended except for patients with concomitant inflammatory bowel disease or recurrent anterior uveitis.</td>
<td>Moderate</td>
</tr>
<tr>
<td>In adults with stable AS receiving treatment with TNF inhibitors and either NSAIDs or slow-acting antirheumatic drugs, continuing treatment with TNF inhibitors alone is conditionally recommended.</td>
<td>Very low</td>
</tr>
</tbody>
</table>

AS: ankylosing spondylitis; LOE: level of evidence; TNF: tumor necrosis factor.

ACR is currently defining the scope of a guideline for psoriatic arthritis. The final publication is expected in 2018.

The National Institute for Health and Care Excellence published guidance in 2016 on TNF-α inhibitors for ankylosing spondylitis and nonradiographic axial spondyloarthritis. The Institute recommended TNF-α inhibitors as options when within their marketing authorizations, for adults with ankylosing spondylitis or nonradiographic axial spondyloarthritis who have failed nonsteroidal anti-inflammatory drugs.

Plaque Psoriasis and Psoriatic Arthritis

American Academy of Dermatology

In 2008, the American Academy of Dermatology released guidelines on the management of psoriasis and psoriatic arthritis. These guidelines addressed the treatment of adult and childhood psoriasis and psoriatic arthritis, including biologics. The guidelines gave a strength of evidence grade of A, for the use of the following TNF inhibitors: adalimumab, etanercept, and infliximab.

National Psoriasis Foundation

In 2010, the National Psoriasis Foundation developed consensus treatment recommendations for erythrodermic or exfoliative psoriasis. These recommendations indicated infliximab and cyclosporine were first-line agents that act rapidly for treatment of this indication. However, the availability of data on the treatment of erythrodermic psoriasis was limited, and the need for further is noted.

The Foundation reviewed Canadian guidelines for the management of plaque psoriasis and updated its guidelines in 2012. The guidelines stated that “Infliximab offers rapid and thorough suppression of
psoriasis,” and can be used as a second- or a third-line treatment option for psoriasis. The guidelines warned that use of TNF inhibitors carries the following safety concerns: serious infection, autoimmune conditions, and lymphoma.

**American Uveitis Society**

In 2014, the American Uveitis Society published evidence-based and consensus recommendations for the use of anti-TNF agents in patients with ocular inflammatory disorders. Literature was searched through April 2013, and approximately 400 publications were reviewed. The panel made the following recommendations (see Table 6).

**Table 6. Recommendations on Use of Anti-TNF Agents to Treat Ocular Inflammatory Disorders**

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>SOR</th>
<th>QOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab and adalimumab can be considered as first-line immunomodulatory agents for the treatment of vision-threatening ocular manifestations of Behçet disease</td>
<td>Strong</td>
<td>Good (infliximab) Moderate (adalimumab)</td>
</tr>
<tr>
<td>Infliximab and adalimumab can be considered as second-line immunomodulatory agents for the treatment of vision-threatening uveitis associated with juvenile idiopathic arthritis.</td>
<td>Strong</td>
<td>Good (infliximab) Moderate (adalimumab)</td>
</tr>
<tr>
<td>Infliximab and potentially adalimumab can be considered as potential second-line immunomodulatory agents for the treatment of vision-threatening ocular inflammatory conditions (eg, posterior uveitis, panuveitis, severe uveitis associated with seronegative spondyloarthropathy, and scleritis) in patients who require immunomodulation and have failed or are not candidates for antimetabolite or calcineurin inhibitor therapy.</td>
<td>Strong</td>
<td>Moderate-to-good</td>
</tr>
<tr>
<td>Infliximab and adalimumab can be considered in these patients in preference to etanercept, which seems to be associated with lower rates of treatment success.</td>
<td>Discretionary</td>
<td>Moderate-to-good Not reported</td>
</tr>
</tbody>
</table>

QOE: quality of evidence; SOR: strength of recommendation; TNF: tumor necrosis factor.

**U.S. Preventive Services Task Force Recommendations**

Not applicable.

**Medicare National Coverage**

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

**Ongoing and Unpublished Clinical Trials**

Some currently unpublished trials that might influence this review are listed in Table 7.
Table 7. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing</td>
<td>A Multisite, Fixed Dose, Randomized, Double-Blind, Placebo-Controlled 12-Week Study Evaluating the Efficacy, Safety, and Tolerability of Adjunctive Infliximab for the Treatment of Bipolar I/II Depression</td>
<td>60</td>
<td>Nov 2017</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

REFERENCES


42. Food and Drug Administration (FDA). Remicade prescribing information. *Remicade (infliximab)*, *Pediatric Ulcerative Colitis* 2013;


**CODES**

<table>
<thead>
<tr>
<th>Codes</th>
<th>Number</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td>96365</td>
<td>Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour</td>
</tr>
<tr>
<td></td>
<td>96366</td>
<td>Each additional hour (list separately in addition to code for primary procedure)</td>
</tr>
<tr>
<td>HCPCS</td>
<td>J1745</td>
<td>Injection, infliximab, 10 mg</td>
</tr>
<tr>
<td></td>
<td>Q5102</td>
<td>Injection, infliximab, biosimilar, 10 mg (for Inflectra, report with modifier ZB - Pfizer/Hospira and for Renflexis, report with modifier ZC - Merck/Samsung Bioepis [effective 01/01/18])</td>
</tr>
<tr>
<td>ICD-10-CM</td>
<td>K50.00-K50.919</td>
<td>Crohn’s disease code range</td>
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<tr>
<td></td>
<td>K51.00-K51.919</td>
<td>Ulcerative colitis code range</td>
</tr>
<tr>
<td></td>
<td>K52.81</td>
<td>Eosinophilic gastritis or gastroenteritis</td>
</tr>
<tr>
<td></td>
<td>K52.9</td>
<td>Noninfective gastroenteritis and colitis unspecified</td>
</tr>
<tr>
<td></td>
<td>L40.50-L40.59</td>
<td>Arthropathic psoriasis code range</td>
</tr>
<tr>
<td></td>
<td>L40.8</td>
<td>Other psoriasis</td>
</tr>
<tr>
<td></td>
<td>M06.80-M06.89</td>
<td>Other specified rheumatoid arthritis code range</td>
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<tr>
<td></td>
<td>M06.9</td>
<td>Rheumatoid arthritis unspecified</td>
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<tr>
<td></td>
<td>M45.0-M45.9</td>
<td>Ankylosing spondylitis code range</td>
</tr>
<tr>
<td>ICD-10-PCS</td>
<td>ICD-10-PCS codes are only for use on inpatient services. There is no specific ICD-10-PCS code for this procedure.</td>
<td></td>
</tr>
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</table>

**Type of Service**
- Prescription
- Drug

**Place of Service**
- Outpatient

**POLICY HISTORY**

<table>
<thead>
<tr>
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<th>Action</th>
<th>Description</th>
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</thead>
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<tr>
<td>02/15/02</td>
<td>Add to Prescription section</td>
<td>New policy.</td>
</tr>
<tr>
<td>10/08/02</td>
<td>Replace policy</td>
<td>Policy revised: new FDA-labeled indication for maintenance therapy</td>
</tr>
<tr>
<td>Date</td>
<td>Action</td>
<td>Notes</td>
</tr>
<tr>
<td>------------</td>
<td>-------------------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>07/17/03</td>
<td>Replace policy</td>
<td>Policy revised: infliximab for ankylosing spondylitis now considered medically necessary. Policy updated with reference to TEC Assessment; additional references added. Treatment of psoriatic arthritis will be addressed in the next revision, scheduled for 3.2003.</td>
</tr>
<tr>
<td>12/17/03</td>
<td>Replace policy</td>
<td>Policy updated; policy statement revised to state that treatment of psoriatic arthritis may be considered medically necessary and supporting discussion and references added.</td>
</tr>
<tr>
<td>09/27/05</td>
<td>Replace policy</td>
<td>Policy revised; new FDA-labeled indications noted; policy statement revised to indicate treatment of acute ulcerative colitis and psoriasis is considered medically necessary. All new references added.</td>
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<tr>
<td>12/14/05</td>
<td>Replace policy –</td>
<td>CPT coding updated.</td>
</tr>
<tr>
<td></td>
<td>coding update only</td>
<td></td>
</tr>
<tr>
<td>06/14/07</td>
<td>Replace policy</td>
<td>Policy updated with literature search through April 2007; policy statements updated to reflect FDA approval in severe psoriasis. References 5-6 added.</td>
</tr>
<tr>
<td>01/08/09</td>
<td>Replace policy</td>
<td>Policy updated with literature search through November 2008, references 1-4 and 11-33 added and other references renumbered. “Off-label use” removed from policy title. FDA-approved uses for TNF-blocking agents infliximab; adalimumab, certolizumab, and etanercept added to policy. Language added to restrict the medically necessary policy statements to use as first-line therapy in specific patients with fistulizing Crohn’s disease and second-line therapy for specific patients with rheumatoid arthritis, Crohn’s disease, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis, and ulcerative colitis. Policy statement revised to indicate Behçet syndrome uveitis, juvenile idiopathic arthritis-associated uveitis, sarcoidosis, Sjögren syndrome, and other off-label uses are considered investigational.</td>
</tr>
<tr>
<td>12/08/11</td>
<td>Replace policy</td>
<td>Policy updated with literature search through October 2011, references 1-3, 6-8, 10-12, 15-25, 27, 32-33, 37-39, 42-48, and 54-67 added; other references deleted or renumbered. The following indications were added to the investigational policy status: age-related macular degeneration, alcoholic hepatitis, Behçet syndrome, depression, diabetic macular edema, erythrodermic or exfoliative psoriasis, intra-articular injections, graft-versus-host disease, juvenile idiopathic arthritis, sacroiliitis, systemic lupus erythematosus, systemic sclerosis, Wegener’s granulomatosis.</td>
</tr>
<tr>
<td>09/13/12</td>
<td>Replace policy</td>
<td>Policy updated with literature search, references 1, 4, 13-14, 18, 24, 28, 30-32, 36-40, 50, 54, 76, and 82-84 added. Hidradenitis suppurativa added to the investigational policy status; remainder of the policy statements unchanged.</td>
</tr>
<tr>
<td>10/10/13</td>
<td>Replace policy</td>
<td>Policy updated with literature search through September 11, 2013, for Crohn's disease noted; updated references for other off-label indications.</td>
</tr>
<tr>
<td>Date</td>
<td>Event/Action</td>
<td>Notes</td>
</tr>
<tr>
<td>------------</td>
<td>--------------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>11/12/15</td>
<td>Replace policy</td>
<td>Policy updated with literature review through October 31, 2015; references 11-12, 61, 109, and 139 added. Policy statements unchanged.</td>
</tr>
<tr>
<td>10/13/16</td>
<td>Replace policy</td>
<td>Policy updated with literature review through August 24, 2016; references 6-9, 17, 29, 38, 45, 52-53, 68, 77, 81, 86, 98, 104, 124, 126, 133, 165, and 170-171 added. Policy statements unchanged.</td>
</tr>
<tr>
<td>04/01/17</td>
<td>Coding update only</td>
<td>Add C9487 for Stelara.</td>
</tr>
<tr>
<td>07/26/17</td>
<td>Replace policy (now local)</td>
<td>Policy statement added for cost effective DMARD alternatives that becomes effective 10/1/2017. Removed erroneous Stelara code.</td>
</tr>
<tr>
<td>10/30/17</td>
<td>Replace local policy</td>
<td>Blue Cross of Idaho adopted changes to local policy as noted. Policy updated with literature review through August 23, 2017; references 37-38 and 147, 149, and 151 added; references 2-5 updated; some references removed. Policy statements unchanged.</td>
</tr>
<tr>
<td>01/30/18</td>
<td>Replace local policy</td>
<td>Blue Cross of Idaho added non-preferred drug, Renflexis, to least cost effective DMARD list.</td>
</tr>
</tbody>
</table>