



BlueCross BlueShield
of Kansas City

An Independent Licensee of the
Blue Cross and Blue Shield Association

Remicade[®] (infliximab)

Policy Number: 5.01.15
Origination: 01/2001

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Policy

BCBSKC will provide coverage for Remicade[®] (infliximab) when it is determined to be medically necessary because the criteria shown below are met.

When Policy Topic is covered

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

Fistulizing Crohn's Disease

- reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients with fistulizing Crohn's disease*.

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

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*. In patients who have had inadequate response to one or more DMARDs (disease-modifying anti-rheumatic drugs (i.e., methotrexate, sulfasalazine.);

Crohn's Disease

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

Ankylosing Spondylitis

- reducing signs and symptoms in patients with active ankylosing spondylitis*; in patients who have not had an adequate response to conventional therapy; (i.e., nonsteroidal anti-inflammatory drugs (NSAIDs), 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 who have had inadequate response to one or more DMARDs* (disease-modifying anti-rheumatic drugs (i.e., methotrexate, sulfasalazine.);

Plaque Psoriasis

- for the treatment of adult patients with chronic severe (i.e., extensive and /or disabling) plaque psoriasis who are candidates for systemic therapy and when topical therapies, other systemic therapies (i.e., methotrexate), and phototherapy are medically less appropriate*;

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 therapy* (i.e., corticosteroids, azathioprine, 6-mercaptopurine).

*Indicates FDA-approved indication.

When Policy Topic is not covered

Other uses of infliximab are considered **investigational**, including, but not limited to:

- arthritis (other than rheumatoid arthritis and psoriatic arthritis);
- Behcet syndrome uveitis;
- cancer cachexia;
- endometriosis;
- giant cell arteritis;
- juvenile idiopathic arthritis-associated uveitis;
- Kawasaki syndrome;
- polyarteritis nodosa;
- polymyalgia rheumatica;
- renal cell carcinoma;
- sarcoidosis;
- sclerosing cholangitis;
- Sjogren syndrome;
- systemic necrotizing vasculitides;
- hidradenitis suppurativa

Considerations

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

This Blue Cross and Blue Shield of Kansas City policy statement is consistent with the Blue Cross and Blue Shield Association Policy number 5.01.15.

Description of Procedure or Service

Tumor necrosis factor (TNF) is a cytokine produced by macrophages and T cells. Its name is based on the original observations 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 alpha blocking agents; etanercept (ENBREL[®], Amgen); adalimumab (HUMIRA, Abbott)[®]; certolizumab (CIMZIA[®], UCB) administered via subcutaneous injection and infliximab (REMICADE[®] Centocor) administered via an intravenous (IV) infusion in the physician's office, outpatient setting, or infusion center. This policy focuses on infliximab that is administered in the physician's office and is thus typically adjudicated under the medical benefit.

The initial labeled indications for infliximab by the U.S. Food and Drug Administration (FDA) included treatment of rheumatoid arthritis, fistulizing Crohn's disease, and inducing remission in patients with moderately to severely active Crohn's disease that has had an inadequate response to conventional therapy. In 2002, the FDA approved an additional indication for *maintaining* clinical remission in Crohn's disease. Maintenance therapy is designed to prevent disease flares in patients with quiescent disease; the drugs most commonly used are azathioprine and 6-mercaptopurine. This new, labeled indication markedly broadens the clinical indications for patients with Crohn's disease. 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 Crohn’s disease who have had an inadequate response to conventional therapy. In September 2006, FDA approved infliximab for patients with chronic severe (i.e., 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 the FDA approval.

As of December 2008, infliximab label indications as compared to label indications for TNF blocking agents; adalimumab, certolizumab, etanercept (1)

Key: CD: Yes; agent has an approved indication; Crohn’s Disease; MTX: Methotrexate; DMARDs: Disease modifying anti-rheumatic drugs

TNF Blocking Agent	Rheumatoid Arthritis	Juvenile Idiopathic Arthritis	Crohn’s Disease	Ankylosing Spondylitis	Psoriatic Arthritis	Plaque Psoriasis	Ulcerative Colitis
infliximab	Yes in combination with MTX	No indication	Yes after treatment failure with conventional therapy fistulizing CD	Yes	Yes	Yes when other systemic therapies are medically less appropriate	Yes treatment failure with conventional therapy
adalimumab	Yes alone or in combination with MTX or DMARDs	Yes ages 4 and older	Yes after treatment failure with conventional therapy and infliximab.	Yes	Yes in combination with DMARDs	Yes when other systemic therapies are medically less appropriate.	No indication
certolizumab	No indication	No indication	Yes after treatment failure with conventional	No indication	No indication	No indication	No indication
etanercept	Yes alone or in combination with MTX	Yes ages 2 and older	No indication	Yes	Yes in combination with MTX when response to MTX alone is inadequate	Yes candidates for systemic therapy or phototherapy.	No indication

On September 4, 2008, the FDA released a FDA ALERT (2) notifying healthcare professionals that histoplasmosis and other invasive fungal infections are not consistently recognized in patients taking tumor necrosis factor- α blockers (TNF blockers), Cimzia (certolizumab pegol), Enbrel (etanercept), Humira (adalimumab) and Remicade (infliximab). This has resulted in delays in appropriate treatment, sometimes resulting in death. The FDA will require the makers of the tumor necrosis factor- α blockers (TNF blockers) to further highlight the information about the risk of invasive fungal infections, such as

histoplasmosis, in the *Boxed Warning* and *Warnings sections* of the drugs' prescribing information and the Medication Guide for patients. The FDA will also require that the makers of the TNF blockers educate prescribers about this risk.

Rationale

In March 2006, the American Gastroenterological Association Institute released a medical position statement on corticosteroids, immunomodulators and infliximab in Inflammatory Bowel Disease on behalf of the American Gastroenterological Association (AGA). These recommendations are intended for adult patients and are based upon the interpretation and assimilation of scientifically valid research. The ideal was to provide evidence based upon prospective, randomized placebo-controlled trials; however when this was not possible, the use of experts' consensus was utilized. The recommendation for infliximab is for the treatment of patients with inflammatory and fistulizing Crohn's disease (CD) that failed to respond to other therapies. (3) In October 2006, the FDA approved expanding the indications for infliximab to include 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 therapy.

In May 2008, the American Academy of Dermatology released guidelines for the management of psoriasis and psoriatic arthritis. These guidelines address the treatment of both adult and childhood psoriasis and psoriatic arthritis including biologics. (4)

Dermatologic Manifestations of Psoriasis

The infliximab multinational psoriatic arthritis controlled trial (IMPACT) was a randomized study of infliximab as a treatment of psoriatic arthritis. (5) A secondary outcome focused on improvements in dermatologic manifestations of psoriasis. A total of 104 patients with psoriatic arthritis participated in this randomized, placebo-controlled and blinded study. Of these, only 39 had significant psoriatic skin lesions, as evidenced by a psoriasis area and severity index (PASI) score of ≥ 2.5 . (The maximum PASI score is 72. The score reflects 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, while patients randomized to infliximab continued to receive active treatment. Changes in the PASI score were analyzed for the 39 patients with skin lesions; 68% of infliximab patients achieved improvement of $\geq 75\%$ in the PASI score at week 16 compared to none in the placebo group. However, interpretation of these results is limited. The sample size was only 39 patients. In addition, patients were recruited to this trial based on arthritic manifestations with previous failure of one or more disease-modifying anti-rheumatic drugs (DMARDs). In contrast, it is not known whether previous therapies had been successful in controlling dermatologic manifestations of psoriasis.

Gottlieb and colleagues 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. (6) In contrast to the IMPACT study, which enrolled patients with a PASI score of ≥ 2.5 , this study was limited to patients with a PASI score of 12 or greater and with psoriatic plaques covering at least 10% of their body surface. The primary endpoint was the proportion of patients who achieved at least 75% improvement in the PASI score from baseline at week 10. At week 10, 72% of patients treated with infliximab (3mg/kg) and 88% of patients treated with infliximab (5 mg/kg) achieved a 75% or greater improvement from baseline in the PASI score, compared to 6% in the placebo group ($p < 0.001$). While no studies directly compared various agents, these positive results were considered similar to that associated with cyclosporine, better than that associated with etanercept (another anti-TNF), and better than other topical agents. Results from this larger trial demonstrated that infliximab is an effective alternative in patients with moderately severe psoriasis who meet their study criteria.

Treatment of Ulcerative Colitis

The recent approval by the U.S. Food and Drug Administration (FDA) of infliximab for the treatment of ulcerative colitis was based in part on the results of ACT 1 and ACT 2 randomized studies. These studies enrolled 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. The ACT 1 trial continued infusions until week 46, with final evaluation at week 54. (7) In contrast, the ACT 2 trial continued infusions until week 22, with final evaluation at week 30. (8) The primary endpoint of both trials was induction of clinical response, while secondary endpoints included clinical remission. Results of these trials have now been presented as abstracts at the 2005 Digestive Disease Week meeting. In both studies, the infliximab group had a significant improvement in both clinical response and clinical remission at all time points studied. Also, a significantly greater percentage of patients in the infliximab group were able to discontinue steroids while in clinical remission. Based on the results of these studies, the FDA designated infliximab for priority review.

2006 – 2007 Update

A literature search was conducted using MEDLINE through April 2007. None of the studies identified alter the conclusions in the policy statements above, which are unchanged. Studies, which should be viewed as preliminary, are being reported on use of infliximab for treatment of refractory Kawasaki syndrome. (9) In addition, a publication reported on positive results from intra-articular injections of infliximab in patients with ankylosing spondylitis. (10)

The FDA has approved infliximab for use in pediatric patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy and for use in patients with chronic severe (i.e., extensive and/or disabling) plaque psoriasis who are candidates for systemic therapy and when other systemic therapies are medically less appropriate.

2008 – 2009 Update

The policy was updated to include both on- and off-label uses of infliximab. The FDA-approved indications have not changed since the 2007 update. A MEDLINE search was conducted for the period March 2007 through December 2008 to update the policy. In addition to its labeled uses, infliximab is being studied in treatment-refractory inflammatory diseases. The discussion here will include only publications reporting the use of infliximab or other TNF-alpha blocking agents in 10 or more patients.

Rheumatoid Arthritis

In March 2007, the Canadian Agency for Drugs and Technologies in Health issued a HTA Technology Report, "Infliximab and Etanercept in Rheumatoid Arthritis; Systematic Review of Long-term Clinical Effectiveness, Safety, and Cost-Effectiveness." The authors concluded infliximab and etanercept used concomitantly with methotrexate have moderate efficacy in the long-term treatment of active RA that is resistant to conventional therapy. The short-term (less than 12 months) safety profile was found acceptable. The long-term safety remains a concern. The economic review shows that costs per quality adjusted life year (QALY) are high (greater than \$100,000 for a QALY) surpassing the generally accepted thresholds for cost-effectiveness. The results suggest infliximab with methotrexate, and etanercept with methotrexate are only cost-effective as second-line therapies after failure with traditional disease modifying anti-rheumatic drugs (DMARDs). (11)

A meta-analysis of 12 randomized, controlled clinical trials suggested a clear benefit of anti-TNF agents over placebo or methotrexate in the treatment of rheumatoid arthritis. Patients with late disease appeared to have higher response, irrespective of the anti-TNF agent used, than patients with intermediate to early disease. Although there have been no head-to-head trials, the authors conclude that infliximab, etanercept and adalimumab have similar overall efficacy in rheumatoid arthritis. (12)

Crohn's Disease

A multicenter open-label randomized controlled trial from Europe of 133 patients with active Crohn's disease who had not been previously treated with corticosteroids, antimetabolites or biological agents and who were assigned either early combined immunosuppression (infliximab + either azathioprine or methotrexate) or conventional management (induction with corticosteroids and sequentially adding antimetabolites [azathioprine or methotrexate] and infliximab) with 2-year follow-up, found that early immunosuppression was more effective than conventional therapy for preventing disease progression. (13) At 26 weeks, 60% vs 36% of the early immunosuppression and conventional treatment groups

were in remission (remission rates were statistically different at 1 year (62% and 42%) but not 2 years). Corticosteroid, but not antimetabolite, usage was lower, and the median time to relapse was longer in the early immunosuppression group (329 days vs 175 days). Safety profiles were similar, although the study was not powered to detect safety differences. A phase III randomized trial of 500 patients with early Crohn's disease is nearing completion. The results are expected to be reported in early 2009; and could alter the treatment approach for Crohn's disease. (14, 15)

A systematic review examined the evidence for the effectiveness of TNF-alpha blocking agents in the maintenance of remission in patients with Crohn's disease refractory to conventional treatments, including corticosteroids and immunosuppressives. In the reviewed randomized controlled trials, patients greater than 18 years old with Crohn's disease who had a clinical response or clinical remission with a TNF-alpha blocking agent, or patients with Crohn's disease in remission but unable to wean corticosteroids, were randomized to maintenance of remission with a TNF-alpha blocking agent or placebo. Outcome measures reported in the primary studies included clinical remission, clinical response, and steroid-sparing effects. Nine studies met all inclusion criteria. Pooled results from 3 randomized controlled trials found that infliximab maintains clinical remission (RR 2.50; 95% CI 1.64 to 3.80), clinical response (RR 2.19; 95% CI 1.27 to 3.75), fistula healing (RR 1.87; 95% CI 1.15 TO 3.04) and has corticosteroid-sparing effects (RR 3.13; 95% CI 1.25 to 7.8), in patients with Crohn's disease responsive to infliximab induction therapy. There is evidence from 2 randomized controlled trials that adalimumab maintains clinical remission to week 54 (RR 3.28; 95% CI 2.13 to 5.06), has higher rates of steroid-free remission at week 26 and week 56 versus placebo (6% placebo, versus 29% adalimumab), and is superior to placebo for maintenance of steroid-free remission to week 54 (RR 4.24; 95% CI 1.57 to 11.47). There was evidence from one randomized controlled trial comparing certolizumab pegol to placebo which found certolizumab pegol to be effective for maintenance of clinical remission (RR 1.68; 95% CI 1.30 to 2.16) and clinical response (RR 1.74; 95% CI 1.41 to 2.13) to week 26.

The authors concluded infliximab 5 mg/kg or 10 mg/kg, given every 8 weeks, is effective for the maintenance of remission and maintenance of fistula healing in patients who have responded to infliximab induction therapy. Adalimumab 40 mg weekly or every other week is effective for the maintenance of remission in patients who have responded to adalimumab induction therapy. Certolizumab pegol 400 mg every 4 weeks is effective for the maintenance of remission in patients who have responded to certolizumab induction therapy. No comparative trials have evaluated the relative efficacy of these agents. Adverse events are similar in the infliximab, adalimumab, and certolizumab groups compared with placebo, but study size and duration generally are insufficient to allow an adequate assessment of serious adverse events associated with long-term use. (16)

A review article examined the evidence base of both established treatments (such as enteral nutrition, corticosteroids, 5-aminosalicylates and immunosuppressive agents) and emerging treatments (such as the anti-tumour necrosis factor-alpha agents, infliximab and adalimumab) used to induce and maintain remission in Crohn's disease. The authors conclude exclusive enteral nutrition is recommended as the first line of treatment for the induction of remission in pediatric CD. Corticosteroids are also effective for inducing remission but may be associated with significant adverse events. Patients with chronically active Crohn's disease may benefit from immunosuppressive agents such as azathioprine and methotrexate. Infliximab is effective for inducing remission in patients who continue to have significant active disease despite the use of conventional treatments. Adalimumab may be indicated for patients who develop a severe allergic reaction to infliximab or those who initially respond to infliximab but subsequently lose their response. Treatments that have been shown to be effective for the maintenance of remission include azathioprine, methotrexate, infliximab and adalimumab. Recent evidence also suggests that long-term enteral nutritional supplementation with patients taking about half of their daily calorie requirements as enteral nutrition may be an effective strategy for the maintenance of remission in CD. (17)

A meta-analysis examined placebo-controlled trials to evaluate safety and efficacy of tumor necrosis factor (TNF) antagonists for Crohn's disease. The primary end points were clinical remission for luminal Crohn's disease and fistula closure at greater than or equal to 2 consecutive visits. Ten studies

evaluated anti-TNF treatment of fistulizing Crohn's disease, involving 776 patients. In overall analysis, anti-TNF therapy was effective for fistula closure only in maintenance trials after open-label induction (mean difference, 16%; 95% CI, 8%-25%; $P < .001$). In 21 studies enrolling 5356 individuals, anti-TNF therapy did not increase the risk of death, malignancy, or serious infection. The authors concluded infliximab, adalimumab, and certolizumab are effective in luminal Crohn's disease. Efficacy of anti-TNF agents other than infliximab in treating fistulizing Crohn's disease requires additional investigations. A longer duration of follow-up and a larger number of patients are required to better assess the safety profile of TNF antagonists in Crohn's disease. (18)

A review article explored conventional and emerging treatments for Crohn's disease and ulcerative colitis. The authors discuss 5-aminosalicylic acid agents (mesalamine, olsalazine) a mainstay in the treatment of both Crohn's disease and ulcerative colitis. Antibiotics may have a limited role in the treatment of colonic Crohn's disease. Steroids continue to be the first choice to treat active disease not responsive to other more conservative therapy. Non-systemic steroids such as oral and rectal budesonide for ileal and right-sided Crohn's disease and distal ulcerative colitis respectively are also effective in mild-moderate disease. 6-mercaptopurine and its prodrug azathioprine are steroid-sparing immunomodulators effective in the maintenance of remission of both Crohn's disease and ulcerative colitis, while methotrexate may be used in both induction and maintenance of CD. Infliximab and adalimumab are anti-TNF agents approved in the US and Europe for the treatment of Crohn's disease, and infliximab is also approved for the treatment of ulcerative colitis. (19)

In conclusion, the clinical data related to the use of TNF blocking agents in the treatment of Crohn's disease indicates infliximab, adalimumab, certolizumab pegol are effective for the maintenance of remission in patients who have responded to induction therapy. The efficacy of anti-TNF agents, other than infliximab, in treating fistulizing Crohn's disease requires additional investigation. Studies with longer duration of follow-up and larger number of patients are required to better assess the long-term safety profile of TNF antagonists in Crohn's disease.

Ankylosing Spondylitis

A review article examined the comparative clinical effectiveness and cost-effectiveness of adalimumab, etanercept and infliximab for the treatment of ankylosing spondylitis. Major electronic databases, unpublished evidence such as conference abstracts, reviews of published economic evaluations, and company submissions to the National Institute for Health and Clinical Excellence (NICE) were reviewed. The assessment was conducted according to accepted procedures for conducting and reporting systematic reviews and economic evaluations. Full economic evaluations that compared 2 or more options for treatment and considered both costs and consequences were eligible for inclusion in the economic literature review. Nine placebo-controlled randomized controlled trials were included in the review of clinical effects. These included 2 studies of adalimumab, 5 of etanercept and 2 of infliximab in comparison with placebo (along with conventional management). No randomized controlled trials directly comparing anti-tumour necrosis factor-alpha (TNF-alpha) agents were identified. Meta-analyses were conducted for data on Assessment in Ankylosing Spondylitis (ASAS) (20, 50 and 70% improvement), mean change in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and mean change in Bath Ankylosing Spondylitis Functional Index (BASFI) at 12 weeks following initiation of anti-TNF-alpha therapy or placebo for all 3 drugs. Meta-analyses were also conducted at 24 weeks for etanercept and infliximab. Each meta-analysis of anti-TNF-alpha therapy demonstrated statistically significant advantages over placebo, although there was no significant difference between individual anti-TNF-alpha agents. At 12 weeks, ASAS 50% responses were 3.6-fold more likely with anti-TNF-alpha treatment than placebo. Compared with baseline, BASDAI scores were reduced by close to 2 points at 12 weeks. Functional scores (BASFI) were reduced at 12 weeks. Six full economic evaluations (2 peer-reviewed published papers, 4 abstracts) were included in the review. The conclusions among economic evaluations were mixed, although the balance of evidence indicates that over short time-frames anti-TNF-alpha therapies are unlikely to be considered cost-effective. The limitations of the clinical outcome data impose restrictions on the economic assessment of cost-effectiveness. Direct unbiased randomized controlled trial evidence is only available in the short term. Current assessment tools are limited and at present BASDAI and BASFI are the best available,

although not designed for, or ideal for, use in economic evaluations. The review of the 3 models submitted to NICE identified a number of inherent flaws and errors. The incremental cost-effectiveness ratios (ICERs) of etanercept and adalimumab were roughly similar, falling below an assumed willingness-to-pay threshold of 30,000 pounds. The ICER for infliximab was in the range of 40,000-50,000 pounds per quality-adjusted life-year (QALY). The short-term (12-month) model developed by this report's authors confirmed the large front-loading of costs with a result that none of the 3 anti-TNF-alpha agents appears cost-effective at the current acceptable threshold, with infliximab yielding much poorer economic results (57,000-120,000 pounds per QALY). The assumptions of the short-term model were used to explore the cost-effectiveness of the use of anti-TNF-alpha agents in the long term.

In conclusion, the review of clinical data related to the 3 drugs (including conventional treatment) compared with conventional treatment plus placebo indicates that in the short term (12-24weeks), the 3 treatments (adalimumab, etanercept and infliximab) are clinically effective in relation to assessment of ASAS, BASDAI and BASFI. Indirect comparisons of treatments were limited and did not show a significant difference in effectiveness between the 3 agents. The short-term economic assessment indicates that none of the 3 anti-TNF-alpha agents is likely to be considered cost-effective at current acceptability thresholds, with infliximab consistently the least favorable option. (20)

Sarcoidosis

An analysis from a previously published randomized trial of 138 patients with pulmonary sarcoidosis was published. The observed treatment benefit in extrapulmonary sarcoidosis patients receiving infliximab for 24 weeks was reported as an improvement in ePOST (extrapulmonary Physician Organ Severity Tool, a metric designed for the present study that summarizes the involvement of 17 organs). While a statistical improvement in group-mean score was noted at 24 weeks, this measure has not been clinically validated and its relationship to clinical outcomes is unknown. The accompanying editorial concluded that "a routine role for infliximab has not been established by these data." (21, 22) Use of infliximab for sarcoidosis is considered investigational.

Uveitis

Four small studies (n = 10 to 13 treated with infliximab) of both multiple etiology uveitis and Behcet's uveitis were published. No control groups were included in these studies, which ranged in follow-up duration from 12-36 months. Visual acuity, inflammation and episodes of recurrent severe uveitis were the outcomes of interest. For the 2 prospective open-label trials, 3 of 10 (30%) patients were free of recurrence at 24 months, and 7 of 12 (58%) patients were free of recurrence at 36 months. (23, 24) These small studies are promising, yet without control groups, they do not provide enough to determine impact on clinical outcomes.

Other Uses

A number of placebo-controlled trials of infliximab were conducted for other indications such as polymyalgia rheumatica (n=51), giant cell arteritis (n=44), endometriosis (n=21), sclerosing colangitis (n=24), and pancreatic cancer cachexia (n=89). (25-29) None of these trials showed a clinical benefit of infliximab in their stated outcomes. While small sample sizes may account for some lack of reported effect due to study power, 2 studies (giant cell arteritis, sclerosing colangitis) were terminated early due to lack of treatment effect at interim analysis. (24, 26) Several observational studies reported negative results as well. A prospective cohort study of 19 patients given infliximab to prevent acute graft-versus-host disease did not do so compared to non-treated controls. (30)

Other publications suggested potentially useful indications. One is a case series of refractory systemic necrotizing vasculitides, where, over 35 months of follow-up, 11/15 patients entered remission and 5/15 patients achieved sustained remission (>6 months). However, 10 patients relapsed after a median of 13 months. (31) One report of 2 phase II trials of infliximab as a treatment for refractory renal cell carcinoma (n=18 treated with 10mg/kg, n=19 treated with 5mg/kg) showed partial response or stable disease with 61% of those receiving the higher dose showing stable disease with a median duration of 7.7 months. One death due to infection was reported as well. (32)

The placebo-controlled studies reporting minimal or no benefit of infliximab treatment in a variety of inflammatory diseases where epidemiologic evidence had suggested benefits are especially sobering, given the drug's toxicities. Well-designed, comparative studies are imperative.

Clinical Trials in Progress

There are 151 trials listed under the key terms "infliximab" on ClinicalTrials.gov. Of these 17 are actively recruiting for the following conditions; psoriasis, Kawasaki Disease, palmoplantar psoriasis, pediatric ulcerative colitis, ulcerative colitis, ankylosing spondylitis, diabetic macular edema, persistent childhood uveitis, obesity, insulin resistance, metabolic syndrome and chronic hepatitis C.(33)

Summary

In summary, there have been no head-to-head comparative trials that have evaluated the relative efficacy of the TNF-blocking agents in the treatment of the various conditions. However, the literature does consider the TNF-blocking agents infliximab, adalimumab, and etanercept to have similar efficacy in rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and plaque psoriasis. For the maintenance of Crohn's disease remission, the TNF-blocking agents infliximab, adalimumab and certolizumab are considered to have clinical efficacy. Infliximab has the additional approved indication for fistula healing. Adalimumab and etanercept are both administered subcutaneously, which may be more advantageous to the intravenous administration of infliximab.

Given the lack of comparative trials and randomized controlled trials for agents across conditions, the evidence does not definitively demonstrate that clinical outcomes are equivalent for the various TNF-blocking agents. The policy statements that infliximab may be considered medically necessary remain unchanged.

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Billing Coding/Physician Documentation Information

J1745 Injection, infliximab, 10mg

Additional Policy Key Words

N/A

Related Topics

N/A

Policy Implementation/Update Information

01/2001	New policy titled Remicade® (infliximab)
01/2002	Review date - no changes made
05/2002	Updated criteria for Rheumatoid Arthritis and Crohn's Disease
01/2003	Review date - no changes made
05/2003	Updated procedure code and criteria for Crohn's Disease
06/2003	Updated criteria for Rheumatoid Arthritis
01/2004	Review date - no changes made
01/2005	Review date - no changes made
08/2005	Updated policy to include criteria for Ankylosing Spondylitis and Psoriatic Arthritis
01/2006	Reviewed - no changes made
01/2007	Updated policy to include criteria for psoriasis
01/2008	Reviewed – no changes made
01/2009	Updated policy to include criteria for pediatric Crohn's Disease
02/2009	Updated policy to reflect BCBSA policy 5.01.15
01/2010	Reviewed – no changes made
01/2011	Reviewed – no changes made
01/2012	Reviewed – no changes made
12/2013	Literature review updated

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