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Medication Policy Manual

Policy No: dru036

Topic: Remicade[®], infliximab

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IMPORTANT REMINDER

This Medical Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medical policy is to provide a guide to coverage. Medical Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Infliximab (Remicade[®]) is a monoclonal antibody that changes the body's immune system. It is used to treat diseases that may be caused or worsened by an overactive immune system, such as rheumatoid arthritis, inflammatory bowel disease or psoriasis.

Policy/Criteria

- I.** Most contracts require prior authorization approval of infliximab prior to coverage. Infliximab may be considered medically necessary in patients when criterion A, B, C, D or E below is met.

- A. Psoriatic arthritis** when the diagnosis is established by a rheumatologist or a dermatologist.

OR

- B. Ankylosing spondylitis** when the diagnosis is established by a rheumatologist.

OR

- C. Rheumatoid arthritis (RA)** when:

1. There is a diagnosis that has been established by a rheumatologist (or by the criteria in Appendix 1).

AND

2. Methotrexate is ineffective after at least a 6 to 12 week treatment course based on documentation which includes one or more of the assessment components listed in Appendix 2 except if methotrexate is contraindicated or not tolerated based on clinical documentation.

AND

3. Infliximab is administered with an oral DMARD (such as methotrexate), unless etanercept, adalimumab, and abatacept have been ineffective, contraindicated, or not tolerated.

OR

- D. Crohn's disease and ulcerative colitis.** Initial authorization for infliximab may be considered medically necessary for:

1. Fistulizing Crohn's disease.

OR

2. Acute treatment of an exacerbation of Crohn's disease or ulcerative colitis when at least one of the following criteria a, b or c below is met:
 - a. Treatment with an adequate course of systemic corticosteroids (e.g., 40 mg to 60 mg prednisone per day for 7 to 14 days) has been ineffective

or is contraindicated.

OR

- b.** The patient has been unable to taper off of an adequate course of systemic corticosteroids without experiencing worsening of disease.

OR

- c.** The patient is experiencing breakthrough disease (e.g., active disease flares) while stabilized for at least 2 months on an immunomodulatory medication (such as azathioprine, mercaptopurine, cyclosporine, or methotrexate).

OR

E. Plaque Psoriasis: Initial authorization for infliximab may be considered medically necessary for patients meeting all of the following criteria 1 through 4:

- 1.** Chart notes support a diagnosis of chronic plaque psoriasis involving at least 10% of the body surface area or causes significant functional disability.

AND

- 2.** The prescribing physician is a dermatologist or rheumatologist.

AND

- 3.** Treatment with phototherapy or photochemotherapy was ineffective, contraindicated, or not tolerated (see Appendix 3).

AND

- 4.** Treatment with at least one oral systemic agent for psoriasis was ineffective or not tolerated, unless all are contraindicated. Examples of oral systemic agents include, but are not limited to, cyclosporine, methotrexate, and acitretin.

II. Administration, Quantity Limitations, and Authorization Period

- A.** Regence does not consider infliximab to be a self-administered medication.
- B.** When prior authorization is approved, infliximab may be authorized in quantities as follows:

- 1. Initial Authorization** – infliximab may be covered in quantities up to 6 infusions in a 6 month period.
 - 2. Continued Authorization** – The maximum number of infusions that may be authorized per year are based on the diagnosis being treated as follows: ^[1]
 - a.** For rheumatoid arthritis, a maximum of 12 infusions in a 1 year period, based on a recommended infusion interval of up to every 4 to 8 weeks.
 - b.** For ankylosing spondylitis, a maximum of 9 infusions in a 1 year period, based on a recommended infusion interval of every 6 weeks.
 - c.** For psoriatic arthritis, a maximum of 7 infusions in a 1 year period, based on a recommended infusion interval of every 8 weeks.
 - d.** For Crohn's disease or ulcerative colitis, a maximum of 7 infusions in a 1 year period, based on a recommended infusion interval of every 8 weeks.
 - e.** For psoriasis, a maximum of 7 infusions in a 1 year period, based on a recommended infusion interval of every 8 weeks.
- C.** Authorization shall be reviewed as follows to confirm that current medical necessity criteria are met and that the medication is effective.
- 1.** Initial authorization shall be reviewed at 6 months.
 - 2.** Continued authorization or re-authorization (after the initial 6 month period) shall be reviewed at least annually, and documentation (including chart notes) indicating that there is disease stability or improvement must be provided.
- III.** Infliximab is considered investigational when used for all other conditions, including, but not limited to:
- A.** Asthma
 - B.** Behçet's Disease
 - C.** Chronic Obstructive Pulmonary Disease (COPD)
 - D.** Chronic Sarcoidosis with Pulmonary Involvement
 - E.** Disc Herniation-Induced Sciatica

- F.** Giant Cell Arteritis
- G.** Hidradenitis suppurativa
- H.** Juvenile Idiopathic Arthritis (i.e. Juvenile Rheumatoid Arthritis)
- I.** Pancreatic cancer cachexia
- J.** Polymyalgia Rheumatica
- K.** Reactive Arthritis/Reiter's Syndrome
- L.** Sclerosing cholangitis
- M.** Undifferentiated spondyloarthropathies
- N.** Uveitis
- O.** Wegener's Granulomatosis

Position Statement

Treatment of rheumatic disorders (rheumatoid arthritis, psoriatic arthritis, juvenile idiopathic arthritis, ankylosing spondylitis) [1, 52-56, 59,63, 67]

- There are many treatments for rheumatic disorders that are effective, have known long-term safety profiles, and are recommended by national treatment guidelines.
- Nonmedical therapies, such as prescribed exercise therapy, physical therapy and weight loss, are important components in any treatment plan for patients suffering from a rheumatic disorder.
- When a systemic medication therapy is needed to manage one of the rheumatic disorders, oral therapies are usually the best value.
 - * Medications to control inflammation, such as nonsteroidal antiinflammatory medications (e.g., ibuprofen, indomethacin, and naproxen) and glucocorticoids (oral and injected into the joint) are effective for the management of symptoms, particularly during the early stages of disease.

- * Orally administered disease-modifying antirheumatic drugs (DMARDs), including methotrexate (MTX), hydroxychloroquine, leflunomide, and sulfasalazine, are effective for decreasing symptoms and slowing disease progression, have a proven track record, and have been the standard of care for many years.
- * Oral therapies have known potential risks. The management of these risks is well established.
- Methotrexate is considered effective in the treatment of RA and the standard reference DMARD to which newer DMARDs (etanercept, anakinra, adalimumab, and leflunomide) are compared for efficacy.
- When non-medical therapies and oral medications are inadequate, the biologic medications (e.g., adalimumab, etanercept, infliximab, or abatacept) may be appropriate. Certolizumab and rituximab have been studied in rheumatoid arthritis, but their role in therapy remains uncertain at this time.
- No studies have shown that any of biologic medications is more effective than another in the treatment of rheumatic disorders, with the exception of indirect evidence that anakinra may be less effective than other alternatives.
 - * The biologic agents can decrease symptoms, help preserve joint functioning, and slow the progression of rheumatic disease.
 - * There have been no reliable, direct-comparative trials that have demonstrated a difference in clinical effect or safety of one agent over another.
 - * Individual responses and tolerability are unpredictable and may vary between patients.
 - * Because responses vary, if one of the biologic agents provides an inadequate response, another biologic medication may yet be effective.
 - * In RA, the best response is seen when methotrexate is used concomitantly with any of the biologics. Infliximab has been shown to be effective only when used with methotrexate. Treatment options other than infliximab should be considered for patients who cannot take methotrexate.

The benefit of medications can be indirectly compared by calculating their number needed to treat (NNT). The number needed to treat is a measure of the chances of a patient achieving a benefit (how many patients need to be treated before a benefit is achieved over a certain period of time). The lower the number needed to treat, the more likely the medication will have benefit.

Table 1 summarizes the chances that certain biologic rheumatologic medications will improve joint pain and stiffness in rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis:

Table 1: Chances of improving joint pain and stiffness by at least 20% after six months of treatment with biologic medications (compared to no treatment). [1, 52-56, 59,63, 67]			
Biologic Medications (when used with methotrexate)	Rheumatoid Arthritis	Psoriatic Arthritis	Ankylosing Spondylitis
adalimumab (Humira) etanercept (Enbrel) infliximab (Remicade)	About 1 in 3 likely to benefit ^a NNT = 3 (Range 2-4)	About 1 in 3 likely to benefit ^a NNT = 3	About 1 in 4 likely to benefit ^a NNT = 4 (Range 3-4)
abatacept (Orencia)	About 1 in 4 likely to benefit ^a NNT = 4 (Range 3-4)	N/A	N/A
anakinra (Kineret)	About 1 in 7 likely to benefit ^a NNT = 7	N/A	N/A
certolizumab (Cimzia)	Uncertain ^b	N/A	N/A
rituximab (Rituxan)	Uncertain ^b	N/A	N/A

^a Benefit = at least 20% improvement in joint pain and stiffness after six months of treatment.

^b The trials for these medications had flaws that make estimating their efficacy uncertain. These flaws included large numbers of patients not completing the clinical trials, not all patients counted in the final results, and uncertainty about whether patients and caregivers were truly unaware of the assigned treatments.

- There is reliable evidence that etanercept, adalimumab, and abatacept (when given with methotrexate) are effective in the management of patients with juvenile idiopathic arthritis (JIA). The design of the clinical studies prevents calculation of “number-needed-to-treat” (NNT) for this use. ^[1, 41, 43]

Efficacy of infliximab in rheumatic disorders

- Compared to placebo and to methotrexate alone, infliximab has been shown to reduce the signs and symptoms, inhibit the radiographic progression, and improve the physical functioning of patients with moderate to severe rheumatoid arthritis. ^[23-26]
- The recommended dose of infliximab for the treatment of rheumatoid arthritis is 3 mg/kg at 0, 2, and 6 weeks and then at every 8 weeks thereafter. ^[1] For patients who have an incomplete response, consideration may be given to adjusting the dose up to 10 mg/kg or treating as often as every 4 weeks. The risk of serious infections is increased at higher doses.
- In various randomized, double-blind, multicenter trials, significantly more ankylosing spondylitis patients receiving infliximab monotherapy showed improvement in signs and symptoms, spinal inflammation and work productivity as compared to patients receiving placebo. ^[12, 27-28]
- The recommended dose of infliximab for the treatment of ankylosing spondylitis is 5 mg/kg at 0, 2, and 6 weeks and then every 6 weeks thereafter. ^[1] There are no data available supporting increased efficacy or safety of higher doses in the treatment of ankylosing spondylitis.
- Compared to placebo, treatment with infliximab significantly reduced signs and symptoms of psoriatic arthritis, inhibited the radiographic progression and improved the quality of life in various double-blind, placebo-controlled, multicenter trials. These effects appear to be sustained though 1 year of treatment. ^[1,13, 29-31, 37-39]
- The recommended dose of infliximab for the treatment of psoriatic arthritis is 5 mg/kg at 0, 2, and 6 weeks and then every 8 weeks thereafter. ^[1] There are no data available supporting increased efficacy or safety of higher doses in the treatment of psoriatic arthritis.

- In a randomized, controlled trial of 508 patients with early rheumatoid arthritis, the ‘BeSt’ study compared two initial monotherapy regimens (MTX initially, followed by OR add-on with other DMARDS) with two initial combination-therapy regimens (MTX + sulfasalazine + tapered high-dose prednisone OR MTX + infliximab).^[35, 36]
 - * At 1 year, initial combination therapy including either prednisone or infliximab resulted in earlier functional improvement and less radiographic damage than did sequential monotherapy or step-up combination therapy. There was no statistical difference in primary endpoints between the two initial combination therapies.^[35]
 - * At 2 years, the difference between the treatment strategies had narrowed and all therapies showed similar clinical improvements. Interestingly, by 2 years 92% of patients in the prednisone-combination therapy group were able to discontinue prednisone due to sustained improvement in disease activity as compared to 74% of patients in the infliximab group who were able to discontinue infliximab.^[36]

Treatment of Crohn’s disease and ulcerative colitis ^[1,52, 54, 60, 61]

- There are many treatments for Crohn’s disease (CD) and ulcerative colitis (UC) that are effective, have known long-term safety profiles, and are recommended by national treatment guidelines.
- Lifestyle interventions, such as smoking cessation and diet modification, are important components of a comprehensive treatment plan for patients suffering from CD.
- When medication therapy is needed to manage CD and UC, oral and topical (administered rectally) therapies are often the best value.
 - * First-line therapies to induce remission include:
 - Patients with CD: oral corticosteroids, methotrexate, aminosalicylates, azathioprine, mercaptopurine.
 - Patients with UC: oral aminosalicylates (e.g., sulfasalazine), topical mesalamine (i.e., rectally administered), topical corticosteroids, or oral corticosteroids, depending on the extent and location of disease.

- Due to the potential for severe adverse effects, the use of conventional corticosteroids such as prednisone is generally reserved for patients with moderate-to-severe disease who failed to respond to first-line therapies. Use is generally limited in duration and frequency.
- Corticosteroids such as prednisone are effective in both patients with Crohn's disease and patients with ulcerative colitis. Dosages in the range of 40 mg – 60 mg/day or 1 mg/kg/day of prednisone or equivalent are effective for induction of remission. ^[49-51]
- * First-line therapies to maintain remission include:
 - Patients with CD: methotrexate and azathioprine.
 - Patients with UC: topical mesalamine (i.e., rectally administered), oral aminosalicylates (e.g., sulfasalazine), topical corticosteroids, or oral corticosteroids, depending on the extent and location of disease.
- When non-medical therapies and oral/topical medications are inadequate, the biologic medications, adalimumab (CD only) or infliximab (CD and UC) may be appropriate. Certolizumab and natalizumab have been studied in CD, but their roles in therapy remain uncertain at this time.
- There is inadequate evidence to show that any one TNF- α inhibitor (including adalimumab, infliximab, and certolizumab) is better than another for the management of patients with moderate-to-severe Crohn's disease.
 - * Generally, these medications result in a remission of disease in about 1 of every 5 to 8 patients when compared with a placebo agent.
 - * There have been no direct comparative trials that have demonstrated a difference in clinical effect or safety of one agent over another.
 - * There is inadequate evidence to establish the efficacy of certolizumab in fistulizing Crohn's disease.
- Because of the risk of serious (sometimes fatal) adverse events with natalizumab, it is recommended that it only be used after other treatment options have failed.
- In this class of medications, only infliximab has been adequately studied in the management of patients with ulcerative colitis.

The benefit of medications can be indirectly compared by calculating their number needed to treat (NNT). The number needed to treat is a measure of the chances of a patient achieving a benefit (how many patients need to be treated before a benefit is achieved over a certain period of time). The lower the number needed to treat, the more likely the medication will have benefit.

Table 2 summarizes the chances that certain biologic medications will improve disease symptoms such as the number and consistency of stools, pain, associated conditions, or weight loss, either initially or as on-going treatment, in patients with Crohn's disease or ulcerative colitis. ^{a,b}

Table 2: Chances of significantly improving symptoms of Crohn’s disease or ulcerative colitis with biologic medications (compared to no treatment). ^[1,52, 54, 60, 61]

Biologic Medications	Crohn’s Disease		Ulcerative Colitis
	Initial Treatment	Ongoing Treatment (6 months of treatment)	Ongoing Treatment (6 months of treatment)
infliximab (Remicade)	About 1 in 3 likely to benefit after 10 weeks of initial treatment NNT = 3	About 1 in 7 patients likely to benefit. NNT = 7 (range 5 - 8)	About 1 in 4 patients likely to benefit. NNT = 4 (range 3 – 5)
adalimumab (Humira)	About 1 in 7 patients likely to benefit after 6 weeks of treatment. NNT = 7 (range 5 – 8)	About 1 in 5 patients likely to benefit. NNT = 5	N/A
certolizumab (Cimzia)	Uncertain ^c		Not studied
natalizumab (Tysabri)	Uncertain ^c		Not studied

^a Crohn’s Disease: Benefit means control of symptoms, otherwise known as “remission”, defined as a total symptom score of no more than 150 on the Crohn’s Disease Activity Index (CDAI), a standard grading system for Crohn’s disease symptoms. This represents a significant improvement in Crohn’s disease symptoms.

^b Ulcerative colitis: Benefit means control of symptoms, otherwise known as “clinical response”, defined as a decrease from baseline in the Mayo score by 30% or more and 3 points or more, accompanied by a decrease in the rectal bleeding sub-score of 1 or more or a rectal bleeding sub-score of 0 or 1. These are standard measures of the severity of symptoms in ulcerative colitis, and represent a significant improvement in ulcerative colitis disease symptoms.

^c The trials for these medications had flaws that make estimating their efficacy uncertain. These flaws included large numbers of patients not completing the clinical trials, not all patients counted in the final results, and uncertainty about whether patients and caregivers were truly unaware of the assigned treatments.

Efficacy of infliximab in Crohn's Disease

- The *Accent I* trial established the safety and efficacy of infliximab in inducing and maintaining clinical remission up to 54 weeks, and in reducing (some cases eliminating) corticosteroid usage. ^[14]
 - * Patients were allowed concomitant therapy with 5-ASA, antibiotics, corticosteroids, 6-mercaptopurine, azathioprine, or methotrexate, if their doses remained stable for a defined period prior to the study.
 - * The effectiveness of 5mg/kg or 10mg/kg maintenance infliximab every 8 weeks did not differ significantly.
- Patients with steroid-dependent Crohn's disease who received infliximab in addition to azathioprine/6-mercaptopurine were found to achieve remission more frequently than azathioprine/6-mercaptopurine alone (57% vs. 29%; OR, 3.3; 95% CI, 1.5 – 7.4; P = 0.003). ^[32]
- Patients who do not respond by Week 14 are unlikely to respond to continued dosing and consideration should be given to discontinuing infliximab in these patients. ^[1]
- The efficacy of infliximab in pediatric Crohn's disease was studied in 112 patients aged 6 to 17 years with moderately to severely active Crohn's disease. All patients received infliximab 5 mg/kg on weeks 0, 2 and 6. Patients responding at week 10 (decrease from baseline of ≥ 15 points on the Pediatric Crohn's Disease Activity Scale-PCDAI) were further randomized to receive infliximab 5 mg/kg either every 8 weeks or every 12 weeks.
 - * At week 10, 88% of patients responded to infliximab and 59% achieved clinical remission (PCDAI score ≤ 10 points).
 - * At week 54, 64% and 56% of patients receiving infliximab every 8 weeks achieved clinical response and remission, respectively, as compared with 33% and 24% of patient receiving every 12 week infusions (P=0.002 and P<0.001, respectively).
 - * Of note, the incidence of infections in patients receiving every 8 week infusions was higher (73.6%) than in patients receiving every 12 week infusions.

Efficacy of infliximab in ulcerative colitis

- Two randomized, double-blind, placebo-controlled, multicenter trials (ACT1 and ACT2) established the efficacy of infliximab for inducing and maintaining remission in adults with ulcerative colitis. ^[17]
- Patients with moderate-to-severe ulcerative colitis received either placebo, 5 mg per kilogram, or 10 mg per kilogram of infliximab at weeks 0, 2, 6, 14, 22, 30, 38, and 46. ^[17] Patients were allowed concomitant treatment with stable doses of aminosalicylates, corticosteroids, and/or immunomodulatory agents.
- As compared to patients receiving placebo, significantly more patients receiving infliximab in both trials achieved a clinical response. ^[17] In addition, patients receiving infliximab required less systemic corticosteroids than patient receiving placebo.
- There were no significant differences in efficacy or quality-of-life scores between the 5 mg per kilogram and 10 mg per kilogram doses of infliximab. ^[17, 41]

Treatment of plaque psoriasis ^[1, 52, 53, 57, 58, 62]

- There are many treatments for psoriasis that are effective, have known long-term safety profiles, and are recommended by national treatment guidelines.
 - * Light therapy, including UVB and PUVA is very effective and safe. UVB therapy can be used at home, as well as at the doctor's office. PUVA may result in long term remissions.
 - * When systemic therapy is needed to manage psoriasis, oral therapies are the best value.
 - Oral therapies, including methotrexate and cyclosporine, have a proven track record and have been the standard of care for many years.
 - Oral medications are effective for most patients, and cyclosporine is known to work rapidly.
 - Oral therapies have known potential risks. The management of these risks is well established.

- When oral medications and phototherapy are inadequate, the biologic medications (e.g., adalimumab, etanercept, infliximab, efalizumab, alefacept) may be appropriate. Each of these biologics been shown to be effective for psoriasis.
- There are no studies showing that any one TNF- α inhibitor (including etanercept, adalimumab, and infliximab) is more effective than another.
- Alefacept and efalizumab are also effective in some patients, but there is indirect evidence that they may be less effective than other alternatives.
- Individual responses and tolerability are unpredictable and may vary between patients.
- Because responses vary, if one of the biologic agents provides an inadequate response, another biologic medication may yet be effective.

Efficacy of biologic agents in plaque psoriasis [1,52, 53, 57, 58, 62]

The benefit of medications can be indirectly compared by calculating their number needed to treat (NNT). The number needed to treat is a measure of the chances of a patient achieving a benefit (how many patients need to be treated before a benefit is achieved over a certain period of time). The lower the number needed to treat, the more likely the medication will have benefit.

Table 3 summarizes the chances that certain biologic medications will improve size and thickness of skin lesions, redness, and itching in moderate to severe plaque psoriasis:

Table 3: Chances of improving of skin lesions, redness, and itching, by 75% after 12 to 16 weeks of treatment with biologic medications (compared to no treatment). [1,52, 53, 57, 58, 62]

Medications	Benefit In Moderate To Severe Plaque Psoriasis
etanercept (Enbrel), adalimumab (Humira), infliximab (Remicade)	About 1 in 3 likely to benefit ^a NNT = 3 (Range 2-4)
alefacept (Amevive)	About 1 in 9 likely to benefit ^a NNT = 9 (Range 2 – 4)
efalizumab (Raptiva)	About 1 in 5 likely to benefit ^a NNT = 5 (Range 3 – 6)

^a Benefit = at least 75% improvement in size and thickness of skin lesions, redness, and itching after 12 to 16 weeks of treatment.

Efficacy of infliximab in plaque psoriasis

- The approval of infliximab for the treatment of severe plaque psoriasis was based primarily on 3 randomized controlled trials.
 - * EXPRESS – evaluated 378 patients who received placebo or infliximab at a dose of 5 mg/kg at weeks 0, 2, and 6. At week 24, the placebo group crossed over to infliximab induction therapy (5 mg/kg), followed by maintenance therapy every 8 weeks. At week 24, more patients receiving infliximab achieved 75% reduction in their “psoriasis index and severity index” score (PASI-75) than did patients receiving placebo. (82% vs. 4%, p<0.0001). [1,30,34]
 - * EXPRESS II – evaluated 835 patients who received placebo or infliximab at doses of 3 mg/kg or 5 mg/kg at Weeks 0, 2, and 6 (induction therapy). At week 16, more patients in either infliximab group (3 mg/kg or 5 mg/kg) achieved PASI-75 than did patients receiving placebo. [1,40]

- At week 14, 595 of the original 627 infliximab patients were randomized to receive their assigned dose (3 mg/kg or 5 mg/kg) at either scheduled, every 8 week intervals or on an “as needed” basis. At 1 year (week 50), the percentage of patients achieving PASI 75 had dropped in all groups, with the patients receiving scheduled infusions doing slightly better than the patients receiving as needed infusions (3 mg/kg: 64.5% q8w vs. 42% prn and 5 mg/kg 78% q8w vs. 57.6% - p-values not reported).^[40]
- * SPIRIT – evaluated 249 patients who had previously received either psoralen plus ultraviolet A treatment (PUVA) or other systemic therapy for their psoriasis. These patients were randomized to receive either placebo or infliximab at doses of 3 mg/kg or 5 mg/kg at Weeks 0, 2, and 6. At week 26, patients judged to be moderate or worse received an additional dose. At end of study, more patients in either infliximab group (3 mg/kg or 5 mg/kg) achieved PASI-75 than did patients in the placebo group (72%, 88% and 6%, respectively; p<0.001 vs. placebo, both groups).^[1]

Use of infliximab in other conditions

ASTHMA

- In a randomized, double-blind, placebo-controlled trial, 38 patients with moderate asthma treated with inhaled corticosteroids were randomized to receive either infliximab 5 mg/kg or placebo at weeks 0, 2, and 6. The primary endpoint was change in morning peak expiratory flow (PEF) at days 50-56 from baseline.^[46]
- The change in PEF from baseline to days 50-56 did not differ significantly between groups, through the number of patients with exacerbations during weeks 0 to 8 did differ significantly (72% in the placebo group vs. 29% in the infliximab group; p=0.01).^[46]
- Further research is needed to determine the risks and benefits of infliximab in asthma, as well as to define its role among the numerous alternatives for treating moderately severe asthma.^[46]

BEHÇET’S DISEASE

- No randomized controlled trials have been published evaluating the use of infliximab in patients with Behçet’s Disease

CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

- In a randomized, double-blind, placebo-controlled trial, 234 patients with moderate to severe COPD were randomized to receive infliximab 3 mg/kg, 5 mg/kg or placebo at weeks 0, 2, 6, 12, 18, and 24. Patients were assessed through week 44. The primary endpoint was change in Chronic Respiratory Questionnaire (CRQ) total score. [44]
- There was no statistical difference in the change in CRQ total score between patients receiving infliximab and patients receiving placebo. [44]

CHRONIC SARCOIDOSIS WITH PULMONARY INVOLVEMENT

- In a randomized, double-blind, placebo controlled trial, Baughman *et al.* randomized 138 patients with chronic pulmonary sarcoidosis to receive infliximab 3 mg/kg, 5 mg/kg or placebo on weeks 0, 2, 6, 12, 18, and 24, then followed the patients through week 52. The primary endpoint was the change from baseline in the % predicted FVC at week 24. [43]
- At week 24, the combined group of patients receiving infliximab had a least-squares mean increase of 2.5% from baseline compared to no change in the placebo group ($p=0.038$). [43]
- Though statistically significant, the clinical relevance of this magnitude of change is unclear, particularly because there was no treatment benefit demonstrated by the other major secondary clinical endpoints. [43]

DISC HERNIATION-INDUCED SCIATICA

- There was no statistical difference in pain relief with infliximab, compared with placebo in a randomized, controlled trial where 40 patients with unilateral sciatic pain and disc herniation were randomized to receive one infusion of either infliximab 5 mg/kg or placebo. At 52 weeks, 67% of patients who received infliximab reported no pain compared with 63% of patients who received placebo ($P= 0.72$). [45]

GIANT CELL ARTERITIS

- In a randomized, placebo-controlled trial, 44 patients with newly diagnosed giant-cell arteritis that was in steroid remission were assigned (2:1) to receive, in addition to ongoing steroid treatment, either infliximab 5 mg/kg or placebo at weeks 0, 2, 6 then every 8 weeks thereafter. At week 22, infliximab therapy did not increase the proportion of patients without relapse (primary endpoint) compared to placebo ($P=0.65$). The authors concluded that infliximab in this clinical setting offered no benefit. [48]

HIDRADENITIS SUPPURATIVA

- No randomized, controlled trials have been published evaluating the use of infliximab in patients with hidradenitis suppurativa.

JUVENILE RHEUMATOID ARTHRITIS (i.e., Juvenile Idiopathic Arthritis)

- An open-label, multicenter, randomized, double-blind, placebo-controlled study failed to demonstrate efficacy of infliximab in treating patients with juvenile rheumatoid arthritis (JRA).^[1, 66]
 - * One hundred twenty-two children with persistent polyarticular JRA despite prior methotrexate (MTX) therapy were randomized to receive MTX plus infliximab 3 mg/kg through week 44, or MTX plus placebo for 14 weeks followed by MTX plus infliximab 6 mg/kg through week 44.
 - * Sixty-four percent of patients in the 3 mg/kg infliximab group achieved responses according to the American College of Rheumatology (ACR) Pediatric 30 (Pedi 30) criteria for improvement at week 14 compared with 49% of the patients receiving placebo. The between-group difference in this primary efficacy end point was not statistically significant (P = 0.12).

PANCREATIC CANCER CACHEXIA

- A multicenter, phase II, placebo-controlled study in 89 patients with stage II-IV pancreatic cancer and cachexia failed to show statistically significant differences in safety or efficacy when compared with placebo.^[65]

POLYMYALGIA RHEUMATICA

- In a randomized, placebo-controlled trial, 51 patients with newly diagnosed polymyalgia rheumatica were assigned to receive tapered oral prednisone plus either placebo or infliximab 3 mg/kg at weeks 0, 2, 6, 14, and 22. The proportion of patients without relapse at week 52 (primary endpoint) did not differ between groups (P=0.80). The authors concluded that infliximab in this setting was of no clinical benefit.^[47]

REACTIVE ARTHRITIS/REITER'S SYNDROME

- No randomized controlled trials have been published evaluating the use of infliximab in patients with reactive arthritis or Reiter's syndrome.

SCLEROSING CHOLANGITIS

- A double-blind, placebo-controlled study in 24 patients with primary sclerosing cholangitis failed to demonstrate efficacy of infliximab in patients with established primary sclerosing cholangitis. ^[64]

UNDIFFERENTIATED SPONDYLOARTHROPATHIES

- No randomized controlled trials have been published evaluating the use of infliximab in patients with undifferentiated spondyloarthropathies.

UVEITIS

- No randomized controlled trials have been published evaluating the use of infliximab in patients with uveitis.

WEGENER'S GRANULOMATOSIS

- No randomized controlled trials have been published evaluating the use of infliximab in patients with Wegener's granulomatosis.

Safety of infliximab

- The incidence of serious adverse events, especially cardiac events and serious infections, may be increased with the use of higher doses of infliximab. ^[1,26]
 - * Doses greater than 5 mg/kg should not be administered to patients with congestive heart failure and infliximab must not be continued in patients who develop new or worsening symptoms of heart failure. ^[1]
 - + For patients who have resided in regions where histoplasmosis or coccidioidomycosis is endemic, the benefits and risks of infliximab treatment should be carefully considered before initiation of infliximab therapy. ^[1]
 - * The risk of serious infections was found to be higher in patients receiving the unapproved induction regimen of 10 mg/kg of infliximab plus methotrexate followed by a 10 mg/kg maintenance regimen for 22 weeks. ^[26]

- Infliximab carries a black box warning regarding the risk of infection.^[1] Tuberculosis, invasive fungal infections, and other opportunistic infections have been observed in patients receiving infliximab therapy. Some of these infections have been fatal.
- Prior to treatment with infliximab, patients should be evaluated for latent tuberculosis infection with a tuberculin skin test.^[1] Treatment of latent tuberculosis infection should be initiated prior to the start of therapy.
- Infliximab also carries a bolded warning regarding the risk of infection.^[1] Infliximab should not be given to patients with a clinically important, active infection and caution should be exercised when considering the use of infliximab in patients with a chronic infection or a history of recurrent infection. Patients should be monitored for signs and symptoms of infection during or after treatment with infliximab and new infections should be closely monitored. If a patient develops a serious infection, infliximab therapy should be discontinued.
- Caution should be exercised before considering the use of infliximab in patients with pre-existing or recent onset of central nervous system demyelinating or seizure disorders.^[1]

Appendix 1: American College of Rheumatology (ACR) Classification Criteria for Establishing the Diagnosis of Rheumatoid Arthritis (RA) ^[21]

Diagnosis of RA requires the presence of at least 4 of 7 criteria below:

1.	Morning stiffness in and around joints lasting more than 1 hour.
2.	Arthritis in at least 1 area in a wrist or proximal interphalangeal (PIP) joint (hands or fingers) for > 6 weeks.
3.	Simultaneous swelling or fluid accumulation in 3 or more joints for > 6 weeks.
4.	Symmetric (bilateral joint) involvement for > 6 weeks.
5.	Presence of rheumatoid nodules.
6.	Positive serum rheumatoid factor.
7.	Radiographic changes typical of RA (erosion or unequivocal bony decalcification in or adjacent to the involved joint) on hand and wrist present.

Appendix 2: American College of Rheumatology (ACR) Assessment Components for Improvement in Rheumatoid Arthritis (RA) ^[22]

-	Tender joint count.
-	Swollen joint count.
-	Patient's assessment of pain.
-	Patient's global assessment of disease activity.
-	Physician's global assessment of disease activity.
-	Patient's assessment of physical function.
-	Acute phase reactant measures (erythrocyte sedimentation rate or C-reactive protein levels).

Appendix 3: Absolute and Relative Contraindications for Phototherapy or Photochemotherapy

Situations where phototherapy may be absolutely or relatively contraindicated include:

-	Type 1 or type 2 skin
-	History of photosensitivity
-	Treatment of facial lesions
-	Presence of premalignant lesions
-	History of melanoma or squamous-cell carcinoma
-	Physical inability to stand for the required exposure time

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Cross References
Enbrel [®] , etanercept dru035
Humira [®] , adalimumab dru081
Kineret [®] , anakinra dru049
Orencia [®] , abatacept dru129
Amevive [®] , alefacept dru088
Raptiva [®] , efalizumab dru104
Cimzia [®] , certolizumab dru160

Codes	Number	Description
CPT	90765	Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour
CPT	90767	Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); additional sequential infusion, up to 1 hour (List separately in addition to code for primary procedure) (Use 90767 in conjunction with 90765)
CPT	90768	Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); concurrent infusion (List separately in addition to code for primary procedure) (Use 90768 in conjunction with 90765)
HCPCS	J1745	Injection, infliximab, 10mg