Nononcologic Uses of Rituximab and Biosimilars

Policy Number: 5.01.24  Last Review: 4/2021

Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for Rituxan and it when it is determined to be medically necessary because the criteria below are met.

When Policy Topic is covered
Rituxan is considered medically necessary in the treatment of the following conditions:

**Rheumatoid Arthritis** (Rituxan and Truxima [rituximab biosimilar] only)

Rituximab for the treatment of adults with rheumatoid arthritis may be considered medically necessary under the following conditions:

1. Rheumatoid arthritis is moderately to severely active (eg, ≥8 swollen and ≥8 tender joints); and
2. Rituximab is administered in combination with methotrexate; and
3. Either:
   a. Patient has had an inadequate response to 1 or more tumor necrosis factor (TNF) inhibitors; or
   b. Patient has had an inadequate response to methotrexate or other conventional synthetic disease-modifying anti-rheumatic drug (DMARD) and is not suitable for treatment with TNF inhibitors (eg, due a recent [eg, within 5 years] history of lymphoma or other malignancy; latent tuberculosis and contraindications to chemoprophylaxis; or previous demyelinating disease).

**Antineutrophil Cytoplasmic Antibody‒Associated Vasculitides (Granulomatosis With Polyangiitis [Wegener Granulomatosis] and Microscopic Polyangiitis)** (Rituxan and rituximab biosimilars)

Rituximab, in combination with glucocorticoids, is considered medically necessary for the treatment of individuals with antineutrophil cytoplasmic antibody–associated vasculitides (ie, granulomatosis with polyangiitis [Wegener granulomatosis] and microscopic polyangiitis).

**Pemphigus vulgaris** (Rituxan only)

Treatment of moderate to severe pemphigus vulgaris in adults.

**Off-Label Indications**
Rituximab may be considered medically necessary for the following off-label indications:

- The following autoimmune hemolytic anemias (AIHA):
a. warm AIHA in corticosteroid-refractory or corticosteroid-dependent patients;
b. cold agglutination syndrome;
• Thrombotic thrombocytopenic purpura (TTP) in patients with refractory disease or relapse (ie, lack of response to plasma exchange therapy and glucocorticoids);
• Churg-Strauss syndrome (eosinophilic granulomatosis with polyangiitis):
  a. first-line treatment in combination with corticosteroids for patients with severe (organ-threatening) disease;
  b. add-on therapy for treatment-refractory disease;
• Factor inhibitors in patients with hemophilia who are refractory to conventional first-line treatments (eg, immune tolerance induction, glucocorticoids with or without cyclophosphamide), preferably as add-on therapy
• Add-on therapy for patients with hepatitis C virus (HCV)‒associated cryoglobulinemic vasculitis who have:
  a. active disease resistant to anti-viral drugs; OR
  b. severe or life-threatening cryoglobulinemic vasculitis;
• Multicentric Castleman disease (first- or second-line therapy);
• Neuromyelitis optica (NMO) for relapse prevention;
The following pemphigoid diseases in treatment-refractory patients:
  a. bullous pemphigoid;
  b. mucous membrane pemphigoid, including ocular cicatricial pemphigoid; and
c. epidermolysis bullosa acquisita;
• Primary Sjögren syndrome that is refractory to glucocorticoids and other immunosuppressive agents;
• Add-on therapy for systemic lupus erythematosus (SLE) refractory to standard first-line treatment;
• Add-on therapy for lupus nephritis refractory to at least 2 standard first-line treatment regimens;
• Systemic sclerosis (scleroderma) in patients refractory to first-line treatment;
• glucocorticoid-refractory chronic graft-versus-host disease; and
• Desensitization of human leukocyte antigen (HLA)‒sensitized renal transplant candidates before transplantation.
• Idiopathic membranous nephropathy

Drug must be sourced from an approved specialty infusion provider

When Policy Topic is not covered
Rituximab is investigational for all other nononcologic uses, including but not limited to:
• idiopathic thrombocytopenic purpura in patients who do not respond to first-line treatments;
• paroxysmal cold hemoglobinuria;
• mixed connective tissue disease (MCTD);
• multiple sclerosis;
• prophylaxis for graft-versus-host disease;
• induction immunosuppressive therapy for kidney transplantation;
• treatment of antibody-mediated rejection (ABMR) in solid organ transplant recipients; and
• treatment of ABMR after pancreatic islet transplantation.
• Treatment of myasthenia gravis
• Treatment of minimal change disease.

Considerations
Rheumatoid Arthritis
A course of rituximab (two 1000 mg intravenous [IV] infusions separated by 2 weeks) is administered every 24 weeks or based on clinical evaluation, but not sooner than every 16 weeks, in combination with methotrexate. Premedication 30 minutes before each infusion with methylprednisolone 100 mg IV or equivalent glucocorticoid is recommended.
Granulomatosis With Polyangiitis (Wegener Granulomatosis) and Microscopic Polyangiitis

Rituximab 375 mg/m² is administered weekly for 4 weeks, in combination with glucocorticoids. Pneumocystis jiroveci pneumonia (PCP) prophylaxis is recommended during treatment and for at least 6 months following the last rituximab infusion. Description of Procedure or Service

Rituximab is a monoclonal antibody against the CD20 antigen on B-lymphocytes. Rituximab reduces pre-B and B-lymphocytes and is successfully used to treat B-cell lymphoma. Over the last decade, rituximab has been used with increased frequency for nononcologic indications, particularly autoimmune diseases that are thought to be B-cell mediated.

Rationale

Rituximab (Rituxan®) is a chimeric murine/human monoclonal antibody directed against the CD20 surface antigen, which is expressed on pre-B and mature B lymphocytes. Rituximab induces lysis of normal and malignant CD20-expressing B cells; possible mechanisms of cell lysis include complement-dependent cytotoxicity and antibody-dependent cell-mediated cytotoxicity.1

B cells are thought to play a role in the pathogenesis of RA and other autoimmune diseases by producing autoantibodies and proinflammatory cytokines and by activating T lymphocytes.1 Rituximab reduces the number of B cells in the peripheral blood and in lymphoid tissues, thereby interrupting pathogenic processes of autoimmune diseases.

Rituximab is administered by IV infusion.

Food and Drug Administration–Approved Uses

Rheumatoid Arthritis
Four randomized controlled trials (RCTs) established the efficacy of rituximab in combination with methotrexate (MTX) for patients with rheumatoid arthritis (RA) who had an inadequate response to 1 or more tumor necrosis factor (TNF) inhibitors. Subsequent publications have confirmed this finding. A 5-year extension study reported sustained improvements in clinical and radiographic outcomes in patients who received at least 1 course of rituximab compared with placebo, although differences in progression of structural damage were not statistically significant. Evidence for use of rituximab in TNF inhibitor-naïve patients is lacking. For patients with an inadequate response to MTX and contraindications to TNF inhibitor therapy, rituximab may be a reasonable option. In the 5-year extension study, adverse event (AE) rates were generally stable over time.

Antineutrophil Cytoplasmic Antibody–Associated Vasculitides (Granulomatosis With Polyangiitis [Wegener Granulomatosis] and Microscopic Polyangiitis)
One double-blind, double-dummy RCT demonstrated the noninferiority of rituximab to cyclophosphamide in patients with newly-diagnosed or relapsing severe granulomatosis with polyangiitis (GPA) (formerly called Wegener granulomatosis) or microscopic polyangiitis (MPA). Both treatments were administered in combination with glucocorticoids. More patients who received a single course of rituximab maintained complete remission for 12 and 18 months compared with patients who continued azathioprine maintenance therapy, although these differences were not statistically significant. An open-label RCT in patients with newly diagnosed antineutrophil cytoplasmic antibody (ANCA) (GPA or MPA)-associated nephropathy showed no difference in sustained remission or serious adverse events (SAEs) at 12 months in patients treated with or without a rituximab-containing induction regimen.

Off-Label Uses

Autoimmune Hemolytic Anemia
Evidence for rituximab in autoimmune hemolytic anemia (AIHA) comprises a small number of patients with primary (idiopathic) and secondary disease. For warm AIHA, case series and case reports describe patients with refractory disease, and an RCT enrolled patients with previously untreated disease. Response rates were 75% to 93%; sustained responses to 3 years were observed; relapses occurred in 5% to 15% of patients. Serious infections were observed in 4% to 15% of patients. For cold agglutination syndrome (CAS), which generally has a poorer response than warm AIHA to first-line corticosteroids, a response rate of 62% was reported. As a potential corticosteroid-sparing agent in warm AIHA and effective treatment for CAS, rituximab may improve health outcomes. Rituximab is not considered a treatment option for paroxysmal cold hemoglobinuria.

**Thrombotic Thrombocytopenic Purpura**
Studies of rituximab in thrombotic thrombocytopenic purpura (TTP) enrolled patients with acquired (anti-ADAMTS13 antibody-positive) TTP. One small phase 2 cohort study in patients with new-onset or relapsed TTP showed no difference in comparison with historical controls in the number of plasma exchange treatments needed to achieve remission. For patients with relapsed or refractory TTP, observational studies (case reports and case series) reported remission in 98% of rituximab-treated patients with a median follow-up of 10 months. This evidence suggests that, despite a small (3%) risk of SAEs with rituximab, some patients treated with plasma exchange who have relapsed or refractory disease may benefit from the addition of rituximab. Because progressive disease is potentially life-threatening and because relapsed and refractory patients have few alternative treatment options, rituximab may be considered medically necessary in this setting. Approximately half of clinical reviewers who provided input when this policy was under review in 2014 supported the use of rituximab in TTP. A single case series of rituximab prophylaxis for recurrent disease provides insufficient evidence for use of rituximab in this setting.

**Churg-Strauss Syndrome (Eosinophilic GPA)**
Evidence for rituximab in Churg-Strauss syndrome comprises case reports and a case series in treatment-refractory patients, all of whom responded to rituximab add-on therapy. Treatment-related AEs were mild; 1 patient developed a testicular seminoma within 1 year of treatment. Because little is known about treatment options for patients refractory to conventional immunosuppressants, and because rituximab has demonstrated efficacy in other ANCA-associated vasculitides (GPA and MPA), rituximab may be considered medically necessary when used as add-on therapy in patients with treatment refractory Churg-Strauss syndrome. Clinical input received when this policy was under review in 2014 also supported the use of rituximab in combination with corticosteroids as first-line treatment for severe (eg, organ-threatening) disease.

**Factor Inhibitors in Hemophilia**
Rituximab for factor inhibitor eradication in congenital hemophilia and acquired hemophilia A has been studied in a small number of patients, primarily in case reports and cohort studies. In immune tolerance induction (ITI)–refractory patients with congenital hemophilia and factor inhibitor, complete remission occurred in 53% of patients who received rituximab alone or in combination with continued ITI; a small cohort study supported combination therapy in the refractory setting. A comparative study in acquired hemophilia A did not find improved response rates in patients treated with rituximab alone or in combination compared with standard cyclophosphamide plus cyclosporine. Evidence does not support rituximab as an alternative to standard treatments for factor inhibitor eradication (ie, ITI in congenital hemophilia and immunosuppression with cyclophosphamide and corticosteroids in acquired hemophilia A). However, evidence suggests that patients who are refractory to these first-line treatments may benefit from rituximab without an increase in AEs. Combination regimens may be preferred. Given the lack of treatment options in refractory patients and the serious, possibly fatal, outcomes if factor inhibitors are not eradicated, rituximab may be considered medically necessary in this setting.

**Hepatitis C Virus–Associated Cryoglobulinemic Vasculitis**
Recent reviews summarized the literature for rituximab to treat hepatitis C virus (HCV)–associated cryoglobulinemic vasculitis. Across 2 RCTS and many observational studies (total N=377), median overall response was approximately 80%. However, these studies were done before the advent of
several new HCV antiviral drugs and pegylated interferon–free drug regimens. More effective antiviral treatments should improve outcomes, eg, virologic and immunologic responses and cure rate of both HCV and associated vasculitis. However, for patients with antiviral-resistant active disease or with severe or life-threatening cryoglobulinemic vasculitis, rituximab in combination with current treatments may improve health outcomes. Viral load and liver function tests should be monitored during rituximab treatment.

**Mixed Connective Tissue Disease**
One case series of 5 patients with mixed connective tissue disorders (MCTDs), 3 of whom achieved partial remission with rituximab, is insufficient to determine the efficacy and safety of rituximab for the treatment of MCTD.

**Multicentric Castleman Disease**
Evidence for rituximab in multicentric Castleman disease comes almost exclusively from the HIV literature, which reflects the epidemiology of the disease. Prospective and retrospective cohort studies reported reduced incidence of subsequent non-Hodgkin lymphoma and substantially improved overall survival (OS, ≥93% at 2 years in 2 studies; 90% at 5 years in 1 study) in rituximab-treated patients compared with non-rituximab-treated unmatched controls. Progression or emergence of Kaposi sarcoma is an associated risk of rituximab treatment, with Kaposi sarcoma recurrence in approximately 30% of patients. No studies comparing rituximab with currently suggested first-line treatment with ganciclovir or valganciclovir were identified. However, given the low-quality evidence supporting this recommendation and aggressive course of multicentric Castleman disease, effective treatment with rituximab may outweigh its associated risks. Therefore, rituximab may be considered medically necessary for multicentric Castleman disease in the first- or second-line setting.

**Multiple Sclerosis**
One RCT in patients with relapsing-remitting multiple sclerosis (MS) showed improvements in magnetic resonance imaging and clinical outcomes at 24 weeks of follow-up. However, methodologic limitations restrict the conclusions that can be based on these data. One well-designed RCT in patients with primary progressive MS demonstrated no effect of rituximab on disease progression.

**Neuromyelitis Optica**
Evidence for rituximab in neuromyelitis optica (NMO) comprises case series, case reports, and retrospective studies in mostly previously-treated patients. Clinically significant reductions in annualized relapse rates, and less often, in disability progression, were observed. In a retrospective review of 90 patients previously treated with MS treatments (eg, interferon and glatiramer acetate), efficacy of rituximab appeared comparable with that of azathioprine and mycophenolate mofetil, considered first-line immunosuppressive drugs for NMO. Based on adverse events reported, safety of rituximab in NMO appeared comparable with safety in other patient populations. A randomized trial comparing rituximab with other treatments may be infeasible given the rarity of NMO and its often severe disease course. Rituximab may therefore be considered medically necessary based on the available evidence for treatment of NMO in patients who are refractory to standard immunosuppressive treatments.

**Pemphigoid and Pemphigus Diseases**
Evidence for rituximab in pemphigoid and pemphigus diseases comprises case reports, case series, and 1 retrospective comparative study in ocular cicatricial pemphigoid. Patients were refractory to previous treatments, but most (75%-100%) responded to rituximab. Infections, including serious and fatal infections, were reported in 4% to 19% of patients, but AE reporting may have been incomplete. Only 3 of 8 pemphigoid diseases were examined in the literature: epidermolysis bullosa acquisita, bullous pemphigoid, and mucous membrane pemphigoid. Although the body of evidence is small, disease progression can lead to serious outcomes (eg, blindness) or death, reported response rates were high, and treatment options in refractory patients are limited. For these reasons, rituximab may be considered medically necessary for treatment of the pemphigoid and pemphigus diseases reviewed in the literature in treatment-refractory patients.
Primary Sjögren Syndrome
Patients with primary Sjögren syndrome who require more than symptomatic treatment for severe glandular or extraglandular disease are generally treated with corticosteroids and immunosuppressive drugs. Rituximab has been studied in a small number of patients in randomized and nonrandomized trials and observational studies. Efficacy of rituximab was not consistently demonstrated, eg, a large (N=120) randomized trial showed no difference in response compared with placebo in mostly untreated patients, and a small (N=41) nonrandomized trial showed statistically significant differences in response compared with disease-modifying anti-rheumatic drugs (DMARDs) in previously treated patients. Incidence of AEs did not appear to be increased above that observed in other patient populations. Given the limited treatment options and potential serious outcomes, including death, for patients with refractory disease, rituximab may be considered medically necessary for these patients. Well-designed randomized trials comparing rituximab with alternative treatments for first-line and second-line therapy of primary Sjögren syndrome are needed.

Systemic Lupus Erythematosus
Evidence for rituximab in patients with refractory systemic lupus erythematosus (SLE) comprises 1 large RCT that did not show improved response rates at 1 year with rituximab add-on therapy; however, a stringent end point may have obscured clinically important treatment effects. Systematic reviews that included mostly cohort studies and case series of refractory patients generally reported higher response rates (25%-91% overall responses) than controlled studies. Rates of SAEs and severe adverse events, mostly infections and infusion or allergic reactions, were 7% to 13%. This evidence suggests that for some SLE patients refractory to first-line treatments, add-on rituximab may improve health outcomes.

Lupus Nephritis
Evidence for rituximab in refractory lupus nephritis (LN) includes 1 RCT that did not show improved overall response rates at 1 year with rituximab add-on therapy; however, this trial may have been underpowered to show an improvement in partial responses (PRs). Summaries of noncomparative studies reported CR and PR rates of 30% to 40% and approximately 35%, respectively, in patients with mostly refractory disease. AEs occurred in approximately 20% of patients. For some patients with refractory LN, add-on rituximab may improve health outcomes. However, because SAEs were observed in these patients (severe infections, febrile neutropenia, posterior reversible leukoencephalopathy), the risk-benefit profile of rituximab is improved when used after failure of 2 standard treatment regimens.

Systemic Sclerosis (Scleroderma)
Evidence for rituximab in treatment-refractory systemic sclerosis comprised observational studies and 1 small, unblinded trial. Rituximab as add-on or monotherapy generally improved skin symptoms and pulmonary function tests; AEs, including sepsis deaths, occurred in 21% to 47% of patients. This evidence suggests that rituximab may improve health outcomes in some patients with treatment-refractory systemic sclerosis. Because second-line treatment options are limited and the consequences of progressive disease may be life-threatening, rituximab may be considered medically necessary for these patients.

Graft-Versus-Host Disease
Rituximab for treatment of steroid-refractory chronic graft-versus-host disease (GVHD) has been examined in cohort studies, which show response in most patients, with sustained response and steroid reduction or discontinuation in some. Treatment options for patients with steroid-refractory GVHD are limited, rituximab may be considered medically necessary in this setting. Evidence for rituximab prophylaxis for GVHD comprises 2 small cohort studies, 1 of which included a contemporaneous control group. Although results suggest that rituximab may reduce the incidence of GVHD, replication in larger, controlled trials is needed. Due to the risk of SAEs with rituximab, improved health outcomes in the prophylactic setting cannot be assumed.
Pretransplant Desensitization
Rituximab has been studied in the setting of solid organ (primarily kidney) transplantation for pretransplant desensitization, induction immunosuppressive therapy, and treatment of antibody-mediated rejection. Several cohort studies in sensitized patients demonstrated good patient and graft survival with rituximab desensitization 3 years after transplant. An RCT comparing desensitization regimens with and without rituximab was terminated due to excess SAEs in the control arm, and 1 study reported no increase in polyomavirus BK-associated nephropathy at 2 years of follow-up. This evidence suggests that health outcomes are improved with rituximab desensitization regimens in sensitized renal transplant candidates.

Antibody-Mediated Rejection
Evidence for rituximab induction to prevent acute antibody-mediated rejection (ABMR) comprised a meta-analysis of 5 very low-quality trials and 1 RCT. Although the meta-analysis indicated reduced ABMR and improved graft survival compared with controls, trial quality was very low. The RCT demonstrated increased mortality in the rituximab group at 3 years of follow-up. Rituximab has not been shown to improve health outcomes when used for induction immunosuppression in kidney transplant recipients.

Small numbers of heart and kidney transplant recipients with ABMR have been treated with rituximab in comparative studies. Although observed improvements in outcomes suggest potential benefit with rituximab, data are retrospective or from small prospective studies. Dose-response studies and larger RCTs with longer follow-up and are needed to demonstrate improved health outcomes with rituximab treatment of ABMR.

A single case report of rituximab for ABMR after pancreatic islet transplantation provides insufficient evidence for use of rituximab in this setting.

References


Billing Coding/Physician Documentation Information

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<td>J9999</td>
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<td>Castleman Disease</td>
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<tr>
<td>D59.1</td>
<td>Other autoimmune hemolytic anemias</td>
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<tr>
<td>D66</td>
<td>Hereditary factor VIII deficiency (includes hemophilia)</td>
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<tr>
<td>D69.3</td>
<td>Immune thrombocytopenic purpura</td>
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  - **J9310**: Rituximab, 100mg
  - **J9999**: Ruxience (rituximab-pvvr)
  - **J9999**: Truxima (rituximab-abbs)
  - **D47.Z2**: Castleman Disease
  - **D59.1**: Other autoimmune hemolytic anemias
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**Additional Policy Key Words**

Policy Number: 5.01.24

**Policy Implementation/Update Information**

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<tr>
<th>Date</th>
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<tr>
<td>05/2006</td>
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</tr>
<tr>
<td>05/2007</td>
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<td>Revised – added Cimzia and Simponi to list of drugs patient may have inadequate response to before Rituxan is considered for coverage.</td>
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<tr>
<td>09/2015</td>
<td>Updated with new indication for IgA vasculitis also known as Henoch-Schonlein purpura as medically necessary</td>
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<td>Policy reviewed—“Idiopathic thrombocytopenic purpura in patients who do not respond to first-line treatments’ moved from medically necessary to investigational indication. Updated References</td>
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<td>Policy updated with literature review thru August 23, 2016. Idiopathic membranous nephropathy was added to medical necessary (off-label indications) statement, and myasthenia gravis and minimal change disease was added to investigational statement.</td>
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<td>05/2018</td>
<td>Policy updated-Policy updated with literature review through August 24, 2017; references 10, 26, 60, 75, 82, 98-102, 135-136, and 145 added. “Antineutrophil cytoplasmic antibody–associated vasculitides” added to second medically necessary statement for clarification. “Treatment-refractory patients” removed from bullet point on pemphigus diseases in medically necessary statement.</td>
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<td>04/2020</td>
<td>Added biosimilars to policy and added pemphigus to list of approved indications and change title to Nononcologic Uses of Rituximab and Biosimilars</td>
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<td>04/2021</td>
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State and Federal mandates and health plan contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The medical policies contained herein are for informational purposes. The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents Blue KC and are solely responsible for diagnosis, treatment and medical advice. No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, photocopying, or otherwise, without permission from Blue KC.