Rituxan® (rituximab)

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

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

Rheumatoid Arthritis
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, \(\geq\) 8 swollen and \(\geq\) 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).

Granulomatosis With Polyangiitis (Wegener Granulomatosis) and Microscopic Polyangiitis
Rituximab, in combination with glucocorticoids, is considered *medically necessary* for the treatment of adults with granulomatosis with polyangiitis (Wegener granulomatosis) and microscopic polyangiitis.

Non-Hodgkin Lymphoma (NHL):
Rituximab, is considered medically necessary for the treatment of adults with NHL under the following conditions:

- Relapsed or refractory, low-grade or follicular, CD20-positive, B-cell NHL as a single agent;
- Previously untreated follicular, CD20-positive, B-cell NHL in combination with first line chemotherapy and, in individuals achieving a complete or partial response to rituximab in combination with chemotherapy, as single-agent maintenance therapy;
- Non-progressing (including stable disease), low-grade, CD20-positive, B-cell NHL as a single agent after first-line CVP chemotherapy; OR
- Previously untreated diffuse large B-cell, CD20-positive NHL in combination with CHOP or other anthracycline-based chemotherapy regimens.
Chronic Lymphocytic Leukemia (CLL)

Rituximab is considered medically necessary for the treatment of adults with CLL under the following conditions:

- In combination with fludarabine and cyclophosphamide (FC), for the treatment of individuals with previously untreated and previously treated CD20-positive CLL.

Limitations of Use: Rituximab is not recommended for use in individuals with severe, active infections.

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;
- Neuromyelitis optica (NMO) that is refractory to at least 1 standard immunosuppressive drug (eg, azathioprine or mycophenolate mofetil);
- The following pemphigoid diseases in treatment-refractory patients:
  - a. bullous pemphigoid;
  - b. mucous membrane pemphigoid, including ocular cicatricial pemphigoid; and
  - c. epidermolysis bullosa acquisita;
- Pemphigus diseases (ie, pemphigus vulgaris, pemphigus foliaceus, and paraneoplastic pemphigus) in treatment-refractory patients;
- Primary Sjögren syndrome that is refractory to corticosteroids 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; and
- Glucocorticoid-refractory chronic graft-versus-host disease; and
- Desensitization of human leukocyte antigen (HLA)–sensitized renal transplant candidates before transplantation;
- Idiopathic membranous nephropathy;
- Acute lymphoid leukemia (induction/consolidation therapy for Philadelphia chromosome-negative ALL for patients aged greater than or equal to 15 years);
- Chronic lymphocytic/small lymphocytic lymphoma;
- Corticosteroid-refractory autoimmune blistering diseases (pemphigus vulgaris, pemphigus foliaceus, bullous pemphigoid, cicatrical pemphigoid, epidermolysis bullosa acquisita and paraneoplastic pemphigus);
Immune thrombocytopenic purpura (ITP)
  - Additional information to support medical necessity review where applicable: Rituximab is medically necessary for the treatment of immune thrombocytopenic purpura when all of the following criteria are met:
    - Diagnosis of immune thrombocytopenic purpura (ITP); AND
    - Documented platelet count < 50 x 10^9 / L; AND
    - History of failure, contraindication, or intolerance to one of the following:
      - Corticosteroids
      - Immune globulin
      - Splenectomy;
  - Multiple sclerosis, last resort treatment of relapsing disease not adequately responsive* to six or more of the following drugs for MS: interferon beta, glatiramer acetate, teriflunomide, dalfampridine, dimethyl fumarate, fingolimod, alemtuzumab, natalizumab, or daclizumab;
    - *For purpose of this policy, failure of an adequate trial of therapy for multiple sclerosis is defined as follows:
      - The member has increasing relapses (defined as two or more relapses in a year, or one severe relapse associated with either poor recovery or MRI lesion progression); or
      - The member has lesion progression by MRI (increased number or volume of gadolinium-enhancing lesions, T2 hyperintense lesions or T1 hypointense lesions); or
      - The member has worsening disability (sustained worsening of Expanded Disability Status Scale (EDSS) score or neurological examination findings).

Lymphocyte-predominant Hodgkin’s Lymphoma;
- Opsoclonus-myoclonus-ataxia associated with neuroblastoma, that is refractory to steroids; chemotherapy and intravenous immunoglobulins;
- Post-transplant lymphoproliferative disorder;
- Relapsed or refractory hairy cell leukemia in persons who have failed at multiple (2 or more) courses of cladribine;
- Waldenström’s macroglobulinemia.

Drug must be sourced from an approved specialty infusion provider.

When Policy Topic is not covered

Rituximab is investigational for all other uses, including but not limited to:
- Paroxysmal cold hemoglobinuria;
- Mixed connective tissue disease (MCTD);
- 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 minimal change disease;
- Acute disseminated encephalomyelitis;
- Acute myeloid leukemia;
- Adrenal gland neoplasm;
- Anti-myelin-associated glycoprotein neuropathy;
- Anti-phospholipid syndrome;
- Aplastic anemia;
- Arthritis associated with inflammatory bowel disease;
- Autoimmune encephalitis (e.g., limbic autoimmune encephalitis, NMDA-receptor antibody encephalitis);
- Autoimmune neutropenia;
- Autoimmune pancreatitis/atrophy of the pancreas;
- Autoimmune polyendocrine syndrome type 1 (APS-1) [also known as autoimmune polyendocrinopathy candidiasis and ectodermal dysplasia (APECED)];
- Autoimmune retinopathy;
- Behcet's disease;
- Bile salt export pump deficiency after liver transplantation;
- Birdshot retinochoroidopathy;
- Bronchiolitis obliterans;
- Cerebral folate deficiency;
- Chronic inflammatory demyelinating polyneuropathy (CIDP)/IgM-associated polyneuropathy;
- Cogan's syndrome;
- Complex regional pain syndrome (reflex sympathetic dystrophy);
- Crescentic IgA nephropathy;
- Dermatomyositis;
- GALOP syndrome (Gait disorder ataxia; Autoantibodies IgM against central myelin antigen Late age of Onset; Polyneuropathy);
- Goodpasture's syndrome
- Granulomatous lymphocytic interstitial lung disease (GLILD);
- Graves ophthalmopathy;
- Factor VIII and IX inhibitors in persons with hemophilia;
- Hashimoto's encephalitis;
- Hemophagocytic lymphohistiocytosis;
- Idiopathic nephrotic syndrome;
- Idiopathic pulmonary fibrosis;
- Immune complex vasculitis;
- IgG4 related sclerosing disease;
- Juvenile dermatomyositis;
- Juvenile rheumatoid arthritis (juvenile idiopathic arthritis);
- Kawasaki disease;
- Langerhans cell histiocytosis;
- Lupus cerebritis;
- Membrano-proliferative nephropathy;
- Membranous glomerulopathy;
- Minimal change nephrosis/Minimal change disease;
- Monoclonal gammopathy of undetermined significance (MGUS) neuropathy;
- Multiple myeloma;
- Myasthenia gravis;
- Myelodysplastic syndromes;
- Necrotizing myopathy;
- Neuroblastoma;
- Neurosarcomatosis;
- Non-autoimmune hemolytic;
- Orbital pseudolymphoma;
- Paraneoplastic myelopathy;
- Paraneoplastic neurologic syndromes;
- Plasma cell leukemia;
- POEMS (Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal gammopathy, and Skin changes) syndrome;
- Polyarteritis nodosa;
• Polymyositis;
• Primary angitis of the central nervous system;
• Psoriatic arthritis;
• Red cell aplasia in thymoma;
• Retroperitoneal fibrosis;
• Rhabdomyosarcoma;
• Rosai-Dorfman disease;
• Sarcoidosis;
• Scleritis;
• Segmental glomerulosclerosis;
• Sinus histocytosis with massive lymphadenopathy disease (SHML);
• Stiff man/stiff person syndrome;
• Thyroid-associated ophthalmopathy;
• Tolosa-Hunt syndrome;
• Uveitis; AND
• Xanthogranuloma.

Rituximab therapy with in combination with other biologicals such as (Arzerra, Enbrel, Humira, Cimzia Simponi, Remicade, Orencia, Stelara, or Kineret) or Cosentyx is considered experimental and investigational.

Anti-chimeric antibody testing and/or chimeric anti-TNF antibody testing for rituximab therapy is considered experimental and investigational because of insufficient evidence in the peer-reviewed literature.

Rituximab use is NOT indicated in patients with:
• A known hypersensitivity to murine products or other components of the formulation;
• Safety and effectiveness have not been established in pediatric patients <18 years old;
• Prior severe infusion reaction (IgE mediated) to rituximab treatment;
• Women who are pregnant or lactating that have not been apprised of the risk associated with rituximab therapy;
• Prior history of progressive multifocal leukoencephalopathy likely due to rituximab therapy
• Undifferentiated cytopenias;
• Combination therapy with cisplatin;
• T-cell lymphomas or plasma cell disorders/multiple myeloma (other than Waldenström’s Macroglobulinemia); AND
• HLA desensitization during transplant with or without IVIG.

Considerations

Rituximab is administered by IV infusion.

Usual dosing of rituximab for FDA-approved uses: For full dosing and administration information (including premedication recommendations) please refer to prescribing information.

Rheumatoid Arthritis: Two 1,000 mg IV infusions separated by 2 weeks in combination with methotrexate.
• Subsequent doses: Administer subsequent doses every 24 weeks or based on clinical evaluation, but not sooner than every 16 weeks

Granulomatosis with polyangiitis (Wegener granulomatosis) and Microscopic polyangiitis:
375 mg/m² IV once weekly for 4 weeks

Non-Hodgkin lymphoma:
• Relapsed or refractory low-grade or follicular, CD20-positive, B-cell non-Hodgkin lymphoma: 375 mg/m² IV once weekly for 4 or 8 doses
• **Re-treatment:** 375 mg/m² IV once weekly for 4 doses

• **Previously untreated follicular, CD20-positive, B-cell non-Hodgkin lymphoma:** 375 mg/m² IV given on day 1 of each cycle of chemotherapy for up to 8 doses

• **Maintenance dosage:** In patients with complete or partial response, initiate rituximab maintenance 8 weeks following completion of rituximab in combination with chemotherapy as a single-agent at a dose of 375 mg/m² by IV once every 8 weeks for 12 doses

• **Nonprogressing low-grade, CD20-positive, B-cell non-Hodgkin lymphoma:** 375 mg/m² IV once weekly for 4 doses every 6 months to a maximum of 16 doses (as a single agent) following completion of 6 to 8 cycles of cyclophosphamide, vincristine, and prednisone chemotherapy

• **Diffuse large B-cell non-Hodgkin lymphoma:** 375 mg/m² IV on day 1 of each cycle of chemotherapy for up to 8 infusions (in combination with CHOP chemotherapy or other anthracycline-based regimen)

**Chronic lymphocytic leukemia (CLL):** 375 mg/m² IV the day prior to the initiation of fludarabine and cyclophosphamide chemotherapy, then 500 mg/m² on day 1 of cycles 2 to 6 (every 28 days).

- **Concomitant therapy:** *Pneumocystis jirovecii* pneumonia and antiherpetic viral prophylaxis is recommended for patients with CLL during treatment and for up to 12 months following treatment as appropriate

- **Concomitant therapy:** Glucocorticoids administered as methylprednisolone 1,000 mg/day IV for 1 to 3 days followed by oral prednisone 1 mg/kg/day (not to exceed 80 mg/day and tapered per clinical need) are recommended to treat severe vasculitis symptoms. This regimen should begin within 14 days prior to or with the initiation of rituximab and may continue during and after the 4-week course of rituximab treatment

- **P. jirovecii** pneumonia prophylaxis is recommended during treatment and for at least 6 months following the last rituximab infusion

- **Subsequent doses:** Safety and efficacy of treatment with subsequent courses of rituximab have not been established

**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. Rixuximab is used for oncologic and non-oncologic indications. Over the last decade, rituximab has been used with increased frequency for non-oncologic indications, particularly autoimmune diseases that are thought to be B-cell mediated.

**Rationale**

Rituximab (Rituxan®) is a genetically engineered chimeric mouse/human monoclonal antibody directed against the CD20 antigen on B-lymphocytes. Rituximab reduces pre- B and B-lymphocytes and is successfully used to treat B-cell lymphoma. Rixuximab is used for oncologic and non-oncologic indications. Over the last decade, rituximab has been used with increased frequency for non-oncologic indications, particularly autoimmune diseases that are thought to be B-cell mediated.

Rituximab binds to lymphoid cells in the thymus, the white pulp of the spleen, and a majority of B lymphocytes in peripheral blood and lymph nodes. However, there appears to be little or no binding to non-lymphoid tissues.
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. Rituximab reduces the number of B cells in the peripheral blood and in lymphoid tissues, thereby interrupting pathogenic processes of autoimmune diseases.

**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-naive 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.

**Wegener Granulomatosis (Granulomatosis With Polyangiitis) and Microscopic Polyangiitis**
One double-blind, double-dummy RCT demonstrated the non-inferiority 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.

**Non-Hodgkin Lymphoma (NHL):**
Non-Hodgkin's lymphoma (NHL) is a cancer of the lymphatic tissue causing enlargement of lymph nodes and generalized symptoms (Wake et al, 2002). It is a heterogeneous condition. Follicular lymphoma behaves in an indolent fashion, with a median survival of 8 to 12 years. However, it is incurable and most patients with the disease will die from it.

According to the literature, management of NHL consists of intermittent treatment when the disease relapses and causes symptoms. The aim is to maximize quality of life by inducing remission, abolishing the symptoms associated with relapse, with minimal treatment side-effects. Cancer-specific treatment is not usually instituted while the patient is asymptomatic ("watchful waiting"). According to available guidelines, first-line therapy of NHL is usually oral chlorambucil (or an equivalent alkylating agent). Second-line treatment is usually an anthracycline-containing chemotherapy regime.

Guidelines from the National Comprehensive Cancer Network (NCCN, 2010) include indications for rituximab in NHL. Rituximab represents a novel approach to treatment of low-grade NHL, targeting malignant cells without the adverse effects associated with chemotherapy. A pivotal study (Linch, 2001) has demonstrated a response rate of 56 % in relapsed or refractory low-grade NHL. The U.S. Pharmacopoeial Convention (2003) has concluded that rituximab is accepted for the following off-label indications: a) as first-line treatment of diffuse aggressive NHL; b) treatment of relapsed or refractory diffuse aggressive NHL; c) first-line treatment of intermediate to high-grade NHL; and d) first-line treatment of low-grade NHL.
Chronic lymphocytic leukemia (CLL):
The U.S. Pharmacopoeial Convention (2002) has concluded that rituximab is also effective for second-line treatment of patients with relapsed or refractory CD20 positive chronic lymphocytic leukemia (CLL). Chronic lymphocytic leukemia is essentially the bloodstream form of NHL, and is the most common type of leukemia. The disease usually progresses slowly and many people with chronic lymphocytic leukemia (CLL) do not need treatment for months or years. Chronic lymphocytic leukemia mainly affects older people and is rare in people under age 40.

Published evidence from Phase I and Phase II trials have shown that rituximab has activity against CLL with acceptable toxicity. Perry and Rasool (2001) stated that "[therapy] with monoclonal antibodies has been evaluated in patients with CLL. The most useful agent in clinical trials so far appears to be CAMPATH-1H, an antibody directed at CD52. Rituximab also is effective as a second-line or third-line treatment and may assume a more prominent role in the future." The National Cancer Institute's PDQ on Chronic Lymphocytic Leukemia (January 2002) states that "CAMPATH-1H and rituximab (monoclonal antibodies) are under clinical evaluation. Higher doses of rituximab than those used for other non- Hodgkin lymphomas are required."

An April 2001 Cancer Care Ontario Evidence Review of rituximab, however, concluded that "[t]he response rates reported for CLL/SLL continue to be lower than for other histologies and appear lower than those reported for other agents used in this disease." A Toronto Regional Cancer Centre Guideline for CLL (2001) states that "When used in routine doses/scheduling, the chimeric anti-CD20 monoclonal antibody rituximab has been disappointing in the management of CLL."

Arampatzis et al (2011) presented a rare case of chronic lymphocytic leukemia(CLL)-associated focal segmental glomerulosclerosis (FSGS) with nephrotic-range proteinuria. A 53-year old Caucasian man, previously healthy, with no history of hypertension, alcohol use or smoking presented with rapid weight gain, massive peripheral edema, and hypertension. Laboratory findings included a white blood cell count of 49,800 cells/mm3 with an absolute lymphocyte count of 47,000 cells/mm3, serum albumin of 2.3 g/dL, urea 65 mg/dL, and creatinine 1.5 mg/dL. A 24-hour urine collection contained 7.1 g protein and significant hematuria. A peripheral blood smear showed mature lymphocytosis and smudge cells. Diagnostic imaging showed mild para-aortic lymphadenopathy with no renal abnormalities. Bone marrow aspiration and trephine biopsy showed diffuse and focal infiltration with B-CLL lymphocytes. Percutaneous renal biopsy revealed total sclerosis in 3/21(14 %) of the glomeruli and focal and segmental solidification and sclerosis in 4/21 (19 %) glomeruli. A regimen of fludarabine, cyclophosphamide and rituximab was successful in inducing remission of the CLL and clinical resolution of the nephritic-range proteinuria. The authors concluded that a multi-disciplinary approach to monitor both the malignancy and the glomerular lesions is crucial for the optimal management of paraneoplastic glomerulonephritis. They noted that although chemotherapy with fludarabine, cyclophosphamide and rituximab successfully treated CLL-associated nephrotic syndrome in this patient, further studies are required to confirm efficacy in this setting.

Acute Lymphoid Leukemia (ALL)
National Comprehensive Cancer Network’s Drugs & Biologics Compendium lists acute lymphoblastic leukemia (ALL) as a recommended (2A recommendation) indication of rituximab -- induction/consolidation therapy for Philadelphia chromosone-negative ALL for patients aged greater than or equal to 40 years as a component of HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) regimen alternating with high-dose methotrexate and cytarabine with rituximab.

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. A number of reports have indicated the usefulness of rituximab in the treatment of subjects with warm agglutinin autoimmune hemolytic anemia not responding to conventional treatment including corticosteroids and splenectomy (Zecca et al, 2001; D’Arena et al, 2006; Gupta et al, 2002; Shanafelt et al, 2003; Mantadakis et al, 2004) and to cold agglutinin disease not responding to conventional treatments (Schollkopf et al, 2006; Berentsen et al, 2004).

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**
In a Cochrane review, Liu and colleagues (2015) stated that hemophilia A and B are inherited coagulation disorders characterized by a reduced or absent level of factor VIII or factor IX respectively. The severe form is characterized by a factor level less than 0.01 international units (IU)/ml. The development of inhibitors in hemophilia is the main complication of treatment, because the presence of these antibodies, reduces or even nullifies the effectiveness of replacement therapy, making it very difficult to control the bleeding. People with inhibitors continue to have significantly higher risks of morbidity and mortality, with considerable treatment costs. Given the wide “off-label” use of rituximab for treating people with hemophilia and inhibitors, its safety and effectiveness need to be evaluated. These investigators evaluated the safety and effectiveness of rituximab for treating inhibitors in people with inherited severe hemophilia A or B. They searched the Cochrane Cystic Fibrosis and Genetic Disorders Group’s Coagulopathies Trials Register, complied from electronic database searches and hand-searching of journals and conference abstract books. They searched the reference lists of relevant articles and reviews and also searched for ongoing or unpublished studies. Date of last search: January 27, 2015. Randomized controlled trials and controlled clinical trials investigating the safety and effectiveness of rituximab for treating inhibitors in people with hemophilia were selected for
No RCTs matching the selection criteria were eligible for inclusion. No RCTs on rituximab for treating inhibitors in people with hemophilia were identified. The authors concluded that they were unable to identify any relevant trials on the safety and effectiveness of rituximab for treating inhibitors in people with hemophilia. The research evidence available is from case reports and case series. They stated that RCTs are needed to evaluate the safety and effectiveness of rituximab for this condition.

D’arena et al (2015) stated that acquired hemophilia A (AHA) is a rare bleeding disorder caused by the development of specific autoantibodies against naturally occurring factor VIII (FVIII). Although about 50% of cases are idiopathic, AHA may be associated with several non-neoplastic conditions, autoimmune disorders, as well as hematological malignancies, such as chronic lymphocytic leukemia and lymphoma. The long-term suppression of inhibitors is one of the mainstays of the treatment of AHA. These investigators provided a systematic description of data available in the literature on the use of rituximab for the treatment of AHA. They performed a search using the indexed online database Medline/PubMed, without temporal limits, matching the words "rituximab" and "acquired h(a)emophilia". Furthermore, additional published studies were identified in the reference list of the publications found in PubMed. The review of the literature confirmed that rituximab may be a safe and useful treatment for AHA. The authors concluded that although rituximab is not a standard therapy for AHA, it may be useful in resistant cases. However, the definitive place of this monoclonal antibody in the therapeutic strategy for AHA (1st or 2nd-line, alone or in combination with other drugs) remains to be determined more precisely and warrants further investigation.

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. Controlled studies are needed to better define the value of rituximab for this indication (Zaja et al, 2003). Consensus Panel Recommendations from the Second International Workshop on Waldenström’s Macroglobulinemia (Gertz et al, 2003) did not list rituximab among effective interventions for symptomatic mixed cryoglobulinemia (MC).

Ahmed and Wong (2007) noted that mixed cryoglobulinemia (CG) is a systemic immune complex-mediated disease that involves small-to-medium vessel vasculitis, provoked by the CG containing immune complexes that precipitate in cold. It is associated with hepatitis C virus (HCV) infection in 80% of patients. Mixed CG-mediated vasculitis can affect the kidney, liver and heart. Laboratory parameters show presence of cryoglobulin, and in most cases of mixed CG, rheumatoid factor IgM kappa. The current treatment strategy of HCV-associated CG includes targeting the viral trigger HCV with a combination of anti-viral medication, interferon-alpha and ribavirin, or the downstream pathogenic events by means of plasmapheresis, steroids or immunosuppression. With multi-organ involvement, the anti-viral therapy may be limited due to severity of renal disease, treatment failure, side effects or contraindications. On the other hand, immunosuppressive therapy may be poorly
tolerated or ineffective. Thus, new treatment options such as rituximab have been proposed as a rescue therapy. These researchers reviewed the literature to evaluate the current evidence in treating HCV-related refractory mixed CG. There have been many published case series and case reports on the use of rituximab in the treatment of HCV-related CG. However, there has been no randomized controlled trial. In the literature, there have been 60 patients with CG treated with rituximab. The male to female ratio was 14:46. A total of 53 patients were HCV-positive; 46 had mixed type II CG, 7 had type III CG, and for 7 the type was not specified. Twenty-five patients had renal involvement ranging from proteinuria, to nephrotic syndrome, to nephritic syndrome, to chronic kidney disease. Eight patients had had a renal transplant and were on immunosuppression. Most patients responded to rituximab, with only 17 of 60 patients relapsing, and 8 of 17 of those were re-challenged with rituximab with a good response. Total follow-up period varied between 3 and 31 months. The authors concluded that rituximab is a suitable rescue therapy in refractory CG associated with HCV. There is evidence supporting the use of rituximab as first-line therapy, as opposed to the proposals of others who would strongly recommend anti-viral therapy. However, a prospective, randomized, controlled trial is needed to assess the safety and effectiveness of rituximab compared with current standard therapy, which includes anti-viral therapy, immunosuppression, as well as plasmapheresis.

Pietrogrande et al (2011) defined a core set of recommendations for the treatment of HCV-associated mixed cryoglobulinemia syndrome (MCS) by combining current evidence from clinical trials and expert opinion. Expert physicians involved in studying and treating patients with MCS formulated statements after discussing the published data. Their attitudes to treatment approaches (particularly those insufficiently supported by published data) were collected before the consensus conference by means of a questionnaire, and were considered when formulating the statements. An attempt at viral eradication using pegylated interferon plus ribavirin should be considered the first-line therapeutic option in patients with mild-moderate HCV-related MCS. Prolonged treatment (up to 72 weeks) may be considered in the case of virological non-responders showing clinical and laboratory improvements. Rituximab (RTX) should be considered in patients with severe vasculitis and/or skin ulcers, peripheral neuropathy or glomerulonephritis. High-dose pulsed glucocorticoid (GC) therapy is useful in severe conditions and, when necessary, can be considered in combination with RTX; on the contrary, the majority of conference participants discouraged the chronic use of low-medium GC doses. Apheresis remains the elective treatment for severe, life-threatening hyper-viscosity syndrome; its use should be limited to patients who do not respond to (or who are ineligible for) other treatments, and emergency situations. Cyclophosphamide can be considered in combination with apheresis, but the data supporting its use are scarce. Despite the limited available data, colchicine is used by many of the conference participants, particularly in patients with mild-moderate MCS refractory to other therapies. Careful monitoring of the side effects of each drug, and its effects on HCV replication and liver function tests is essential. A low-antigen-content diet can be considered as supportive treatment in all symptomatic MCS patients. Although there are no data from controlled trials, controlling pain should always be attempted by tailoring the treatment to individual patients on the basis of the guidelines used in other vasculitides. The authors concluded that although there are few controlled randomized trials of MCS treatment, increasing knowledge of its pathogenesis is opening up new frontiers. The recommendations provided may be useful as provisional guidelines for the management of MCS.

De Vita et al (2012) conducted a long-term, prospective, randomized controlled trial evaluating RTX therapy for severe mixed cryoglobulinemia (MC) or cryoglobulinemic vasculitis (CV). A total of 59 patients with CV and related skin ulcers, active glomerulonephritis, or refractory peripheral neuropathy were enrolled. In CV patients who also had HCV infection, treatment of the HCV infection with anti-viral agents had previously failed or was not indicated. Patients were randomized to the non-RTX group (to receive conventional treatment, consisting of 1 of the following 3: glucocorticoids; azathioprine or cyclophosphamide; or plasmapheresis) or the RTX group (to receive 2 infusions of 1 g each, with a lowering of the glucocorticoid dosage when possible, and with a second course of RTX at relapse). Patients in the non-RTX group who did not respond to treatment could be switched to the RTX group. Study duration was 24 months. Survival of treatment at 12 months (i.e., the proportion of patients who continued taking their initial therapy), the primary end point, was statistically higher in the RTX group (64.3 % versus 3.5 % [p < 0.0001]), as well as at 3 months (92.9 % versus 13.8 % [p < 0.0001]), 6
months (71.4 % versus 3.5 % [p < 0.0001]), and 24 months (60.7 % versus 3.5 % [p < 0.0001]). The Birmingham Vasculitis Activity Score decreased only after treatment with RTX (from a mean +/- SD of 11.9 +/- 5.4 at baseline to 7.1 +/- 5.7 at month 2; p < 0.001) up to month 24 (4.4 +/- 4.6; p < 0.0001). Rituximab appeared to be superior therapy for all 3 target organ manifestations, and it was as effective as conventional therapy. The median duration of response to RTX was 18 months. Overall, RTX treatment was well-tolerated. The authors concluded that rituximab monotherapy represents a very good option for severe CV and can be maintained over the long-term in most patients.

Sneller et al (2012) conducted a single-center, open-label, randomized controlled trial of rituximab (375 mg/m(2)/week for 4 weeks) compared to the best available therapy (maintenance or increase in immunosuppressive therapy) for HCV-associated CV in patients in whom anti-viral therapy had failed to induce remission. The primary end point was disease remission at 6 months from study entry. A total of 24 patients were enrolled (12 in each treatment group). Baseline disease activity and organ involvement were similar in the two groups. Ten patients in the rituximab group (83 %) were in remission at study month 6, as compared with 1 patient in the control group (8 %), a result that met the criterion for stopping the study (p < 0.001). The median duration of remission for rituximab-treated patients who reached the primary end point was 7 months. No adverse effects of rituximab on HCV plasma viremia or on hepatic transaminase levels were observed. The authors concluded that rituximab was a well-tolerated and effective treatment in patients with HCV-associated CV in whom anti-viral therapy failed to induce remission.

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
There is emerging evidence for the effectiveness of rituximab in Castleman's disease (CD). Two clinical classifications of CD have been described: unicentric (unifocal or localized) and multi-centric (multi-focal or generalized) (Dispenzieri and Gertz, 2005). The uni-centric presentation responds well to surgical resection and is associated with a benign course. The multi-centric presentation requires systemic therapy and prognosis is guarded. Associated systemic symptoms are common. There is an increased incidence of CD in patients with HIV. Evidence for rituximab in multicentric Castleman disease comes almost exclusively from the HIV literature, which reflects the epidemiology of the disease. The human herpes virus-8 is associated with nearly all of the HIV-associated CD cases and nearly 50 % of non-HIV cases. Interleukin (IL)-6 has also been shown to play a significant role in the pathogenesis of the disease. Paraneoplastic and autoimmune entities are not uncommon in the disorder. Variable benefit has been achieved with rituximab (Dispenzieri and Gertz, 2005; Ide et al, 2006; Casquero et al, 2006; Marcelin et al, 2003). Patients with CD are at increased risk for developing frank malignant lymphoma.

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.

More than 80 % of individuals with multiple sclerosis (MS) experience a relapsing-remitting disease course (He et al., 2013). Approximately 10 years after disease onset, an estimated 50 % of individuals with relapsing-remitting MS (RRMS) convert to secondary progressive MS. Multiple sclerosis causes a major socioeconomic burden for the individual patient and for society. Effective treatment that reduces relapse frequency and prevents progression could impact both costs and quality of life and help to reduce the socioeconomic burden of MS. Alternative and more effective MS treatments with new modes of action and good safety are needed to expand the current treatment repertoire. It has been shown that B lymphocytes are involved in the pathophysiology of MS and rituximab lyses B-cells via complement-dependent cytotoxicity and antibody-dependent cellular cytotoxicity. Current clinical trials are evaluating the role of rituximab as a B-cell depletion therapy in the treatment of RRMS.

He et al (2013) completed an update of the Cochrane review of rituximab for RRMS. The safety and effectiveness of rituximab, as monotherapy or combination therapy, versus placebo or approved disease-modifying drugs (DMDs) (interferon-β (IFN-β), glatiramer acetate, natalizumab, mitoxantrone, fingolimod, teriflunomide, dimethyl fumarate, alemtuzumab) to reduce disease activity for people with RRMS were assessed. The Trials Search Co-coordinator searched the Cochrane Multiple Sclerosis and Rare Diseases of the Central Nervous System Group Specialized Register. The authors checked the references in identified trials and manually searched the reports (2004 to August 2013) from neurological associations and MS societies in Europe and America. They also communicated with researchers who were participating in trials on rituximab and contacted Genentech, BiogenIdec and Roche. The systematic review included all randomized, double-blind, controlled parallel group clinical trials with a length of follow-up equal to or greater than 1 year evaluating rituximab, as monotherapy or combination therapy, versus placebo or approved DMDs for patients with RRMS without restrictions regarding dosage, administration frequency and duration of treatment. The authors used the standard methodological procedures of The Cochrane Collaboration. Two review authors independently assessed trial quality and extracted data. Disagreements were discussed and resolved by consensus among the review authors. Principal investigators of included studies were contacted for additional data or confirmation of data. One trial involving 104 adult RRMS patients with an entry score less than or equal to 5.0 on the Expanded Disability Status Scale (EDSS) and at least 1 relapse during the preceding year was included. This trial evaluated rituximab as monotherapy versus placebo, with a single course of 1,000 mg intravenous rituximab (on day 1 and day 15). A significant attrition bias was found at week 48 (24.0 %). Patients receiving rituximab had a significant reduction in total number of gadolinium-enhancing lesions at week 24 (mean number 0.5 versus 5.5; relative reduction 91 %) and in annualized rate of relapse at week 24 (0.37 versus 0.84) but not at week 48 (0.37 versus 0.72). Disability progression was not included as an outcome in this trial. More patients in the rituximab group had adverse events within the 24 hours after the first infusion (78.3 % versus 40.0 %), such as chills, headache, nausea, pyrexia, pruritus, fatigue, throat irritation, pharyngolaryngeal pain, and most were mild-to-moderate events (92.6 %). The most common infection-associated adverse events (greater than 10 % in the rituximab group) were nasopharyngitis, upper respiratory tract infections, urinary tract infections and sinusitis. Among them, only urinary tract infections (14.5 % versus 8.6 %) and sinusitis (13.0 % versus 8.6 %) were more common in the rituximab group. One ongoing trial was identified. The authors concluded that there is not sufficient evidence to support the use of rituximab as a disease-modifying therapy for RRMS because only 1 randomized controlled trial (RCT) was included. The quality of the study was limited due to high attrition bias, the small number of participants, and short follow-up. The authors concluded that the beneficial effects of rituximab for RRMS remain inconclusive. However, short-term treatment with a single course of rituximab was safe for most patients with RRMS. Mild-to-moderate infusion-associated adverse events were common, as well as nasopharyngitis, upper respiratory tract infections, urinary tract infections and sinusitis. The potential...
benefits of rituximab for treating RRMS need to be evaluated in large-scale studies that are of high quality along with long-term safety.

In a phase II, double-blind, 48-week clinical trial involving 104 patients with relapsing-remitting multiple sclerosis, Hauser et al (2008) assigned 69 patients to receive 1,000 mg of intravenous rituximab and 35 patients to receive placebo on days 1 and 15. The primary end point was the total count of gadolinium-enhancing lesions detected on magnetic resonance imaging scans of the brain at weeks 12, 16, 20, and 24. Clinical outcomes included safety, the proportion of patients who had relapses, and the annualized rate of relapse. As compared with patients who received placebo, patients who received rituximab had reduced counts of total gadolinium-enhancing lesions at weeks 12, 16, 20, and 24 (p < 0.001) and of new gadolinium-enhancing lesions over the same period (p < 0.001); and these results were sustained for 48 weeks (p < 0.001). As compared with patients in the placebo group, the proportion of patients in the rituximab group with relapses was significantly reduced at week 24 (14.5 % versus 34.3 %, p = 0.02) and week 48 (20.3 % versus 40.0 %, p = 0.04). More patients in the rituximab group than in the placebo group had adverse events within 24 hours after the first infusion, most of which were mild-to-moderate events; after the second infusion, the numbers of events were similar in the 2 groups. The authors concluded that a single course of rituximab reduced inflammatory brain lesions and clinical relapses for 48 weeks. However, the authors noted that this phase II study was not designed to evaluate long-term safety or to detect uncommon adverse events. They stated that the safety and effectiveness of rituximab for the treatment of multiple sclerosis need to be validated by larger and longer-term controlled studies. MacFarland (2008) noted that a phase II clinical trial leaves many questions unanswered including the duration of the treatment effect, the effect of progression of disability, and most importantly the types of adverse events that may occur at low frequency. Issues of long-term safety of rituximab must still be addressed, given reports to the FDA of progressive multifocal leukoencephalopathy in patients with lupus who were treated with rituximab.

Genentech, Inc. (South San Francisco, CA) reported that a Phase II/III randomized, double-blind, placebo-controlled, multi-center study to evaluate the efficacy, safety and tolerability of 4 courses of rituximab for primary-progressive multiple sclerosis (PPMS) did not meet its primary endpoint as measured by the time to confirmed disease progression during the 96-week treatment period. A total of 439 patients were randomized 2:1 to receive either 4 treatment courses of rituximab 6 months apart or placebo. MRI evaluations were conducted at baseline, weeks 6, 48, 96 and 122. The incidence of overall adverse events was comparable between rituximab and placebo treatment groups. Serious adverse events were 16.4 % in the rituximab arm versus 13.6 % in the placebo arm, with an incidence of serious infections of 4.5 % compared with less than 1.0 % respectively. Infectious events (10 %) reported in either group included upper respiratory and urinary tract infections. Most infectious events in the rituximab arm were reported as mild to moderate in severity, though events of greater severity were reported more frequently in patients receiving rituximab. There were more infusion-related reactions with rituximab, the majority of which were mild to moderate in severity (Genentech, 2008).

A randomized controlled trial (Hawker et al, 2009) of rituximab for PPMS found no significant difference between rituximab and placebo in time to confirmed disease progression, the primary study endpoint. Subgroup analysis suggested that rituximab may have a significant effect on time to confirmed disease progression in younger patients; however, this finding would need to be confirmed in clinical trials designed to test this hypothesis. In an accompanying editorial, Hartung and Aktas (2009) stated that "having failed to reach the primary endpoint, rituximab joins the league of drugs that showed disappointing or inconclusive results in therapy trials in PPMS". Regarding the findings of the subgroup analysis, Hartung and Aktas (2009) commented that "[t]hus, these results suggest that, before jumping to conclusions, a note of caution needs to be added to these types of subgroup analyses. They are of a purely exploratory character and definitely should not guide therapeutic decisions in current neurological practice. However, they do offer important insights into the pathobiology of the disease as correctly pointed out by Hawker and colleagues in their discussion of the findings obtained"

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. 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.

Neuromyelitis Optica Study Group (NEMOS) stated that NMO Testing of AQP4-Ab is essential and is the most important test in the diagnostic work-up of suspected NMO, and helps to distinguish NMO from other autoimmune diseases. In addition, imaging techniques, particularly magnetic resonance imaging of the brain and spinal cord, are obligatory in the diagnostic workup. The NEMOS stated that it is important to note that brain lesions in NMO and NMOSD are not uncommon, do not rule out the diagnosis, and show characteristic patterns. Other imaging modalities such as optical coherence tomography are proposed as useful tools in the assessment of retinal damage. Therapy of NMO should be initiated early. The NEMOS suggested azathioprine and rituximab as first-line treatments, the latter being increasingly regarded as an established therapy with long-term efficacy and an acceptable safety profile in NMO patients. Other immunosuppressive drugs, such as methotrexate, mycophenolate mofetil and mitoxantrone, are recommended as second-line treatments. Promising new therapies are emerging in the form of anti-IL6 receptor, anti-complement or anti-AQP4-Ab biologicals.

In an open label study, Cree et al (2005) reported their findings of 8 patients with worsening neuromyelitis optica who were treated with rituximab. Treatment was well-tolerated; 6 of 8 patients were relapse free and median attack rate declined from 2.6 attacks/patient/year to 0 attacks/patient/year (p = 0.0078). Seven of 8 patients experienced substantial recovery of neurological function over 1 year of average follow-up. The pre-treatment median Expanded Disability Status Scale score was 7.5, and at follow-up examination was 5.5 (p = 0.013). These investigators noted that the apparently robust effects of rituximab deserve further investigation through controlled trials.

In a prospective, open-label study, Kim and colleagues (2011) evaluated the safety and effectiveness of repeated rituximab treatment based on the assessment of peripheral circulating memory B cells over 24 months in patients with relapsing neuromyelitis optica (NMO). A total of 30 patients with relapsing NMO or NMO spectrum disorder were included in this study. Treatment protocol of rituximab consisted of an induction therapy (375 mg/m² once-weekly for 4 weeks or 1,000 mg infused twice, with a 2-week interval between the infusions) followed by maintenance therapy. The maintenance therapy was repeated treatment with rituximab (375 mg/m², once) whenever the frequency of reemerging CD27+ memory B cells was more than 0.05 % in peripheral blood mononuclear cells by flow cytometric analysis. Main outcome measures included annualized relapse rate, disability (Expanded Disability Status Scale score), anti-aquaporin 4 antibody level, and safety of rituximab treatment. Of 30 patients, 28 showed a marked reduction in relapse rate while taking rituximab over 24 months. The relapse rate was reduced significantly, by 88 %, and 70 % of patients became relapse-free over 24 months. Disability either improved or stabilized in 97 % of patients. Anti-aquaporin 4 antibody levels declined significantly following treatment with rituximab, consistent with the clinical response and the effect on CD27+ memory B cells. Repeated treatment with rituximab was generally well-tolerated, and no clinically relevant adverse event leading to discontinuation of treatment was observed. The authors concluded that repeated treatment with rituximab appeared to produce consistent and sustained efficacy over 24 months with good tolerability in patients with NMO.

Pellkofer et al (2011) performed a prospective long-term cohort study of 10 patients with NMO who were treated up to 5 times with rituximab as a second-line therapy. Clinical examinations, B-cell counts, and serum concentrations of BAFF (B-cell activating factor of the TNF family; also called TNFSF13b), APRIL (a proliferation-inducing ligand; also called TNFSF13), AQP4-ab, and immunoglobulin levels were measured every 3 months. Repeated treatment with rituximab led to sustained clinical stabilization in most patients with NMO. Disease activity correlated with B-cell depletion, but not clearly with AQP4-ab or levels of APRIL. BAFF levels increased after application of rituximab and indicated persisting efficacy of the drug but did not correlate with disease activity. Overall, rituximab was well-tolerated even after up to 5 consecutive treatment courses; however,
several severe adverse reactions were observed. The authors concluded that these data indicated that long-term therapy with rituximab is effective in NMO as a second-line therapy and has an acceptable safety profile. Re-treatment with rituximab should be applied before re-appearance of circulating B cells.

**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.

Rituximab has been increasingly used in autoimmune blistering dermatoses, mainly in pemphigus. Joly et al (2007) found that a single cycle of rituximab is an effective treatment for pemphigus vulgaris of pemphigus foliaceus. The investigators studied 21 patients with pemphigus vulgaris or pemphigus foliaceus whose disease had not responded to an 8-week course of 1.5 mg of prednisone per kilogram of body weight per day (corticosteroid-refractory disease), who had had at least 2 relapses despite doses of prednisone higher than 20 mg per day (corticosteroid-dependent disease), or who had severe contraindications to corticosteroids. Patients were treated with 4 weekly infusions of 375 mg of rituximab per square meter of body-surface area. Eighteen of 21 patients had a complete remission at 3 months after the end of treatment. In 8 of the 18 patients, this remission was maintained without corticosteroid or immunosuppressive therapy after a median follow-up of almost 3 years. One patient developed pyelonephritis and another died of septicemia. The investigators concluded that a single cycle of rituximab is an effective treatment for pemphigus (Joly et al, 2007). The investigators warned that, because of its potentially severe side effects, its use should be limited to the most severe types of the disease. An editorialist noted that this study demonstrated the value of a multi-center approach to accomplish relevant clinical research in orphan diseases such as pemphigus (Diaz, 2007).

Kasperkiewicz et al (2011) concluded that adjuvant rituximab is effective and well-tolerated not only in patients with pemphigus but also with pemphigoid. A total of 17 patients with refractory autoimmune blistering dermatoses (pemphigus vulgaris, n = 8; pemphigus foliaceus, n = 2; bullous pemphigoid, n = 2; mucous membrane pemphigoid, n = 5) were treated 4 times with rituximab at weekly or bi-weekly intervals. Six of 8 patients with a relapse after this regimen received rituximab again twice in a 2-week interval. The investigators reported that all lesions cleared in 14 patients (7 pemphigus vulgaris, 2 pemphigus foliaceus, 2 bullous pemphigoid, 3 mucous membrane pemphigoid), whereas partial healing was found in 3 others (1 pemphigus vulgaris, 2 mucous membrane pemphigoid). Relapses occurred in 8 patients (5 pemphigus vulgaris, 2 pemphigus foliaceus, 1 bullous pemphigoid). Re-treatment with rituximab again resulted in complete (2 pemphigus vulgaris, 1 pemphigus foliaceus, 1 bullous pemphigoid) or partial (2 pemphigus vulgaris) remission.

Peterson and Chan (2009) performed a survey of 71 consecutive patients with autoimmune blistering diseases treated with rituximab from initial use up to 2007, using the PubMed database. The authors stated that a heterogeneous group of patients, including 51 patients with pemphigus vulgaris, 1 with pemphigus vegetans, 9 with pemphigus foliaceus, 5 with paraneoplastic pemphigus, 4 with epidermolysis bullosa acquisita, and 1 with both bullous pemphigoid and graft-versus-host disease was included in this survey. The authors reported that, overall, the monoclonal antibody seems to be effective in that 69% of patients showed complete response, 25% of patients showed partial response, whereas 6% of patients showed progressive disease. Six deaths occurred in association with the
treatment, with 4 of these deaths in patients with paraneoplastic pemphigus, a disease characteristically resistant to conventional medication and with a high mortality rate.

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.

Primary Sjögren's syndrome (pSS) is an autoimmune disorder affecting exocrine glands; however, a subgroup of pSS patients experience systemic extra-glandular involvement leading to a worsening of disease prognosis (Carubbi, et al., 2013). Current therapeutic options are mainly empiric and often translated by other autoimmune diseases. In the last few years growing evidence suggests that B-cell depletion by rituximab (RTX) is effective also in pSS. Patients with early active disease appear to be those who could benefit the most from RTX.

A systematic evidence review concluded that further clinical trials are necessary to establish the efficacy of rituximab in primary Sjögren syndrome. Ramos-Casals, et al (2010) searched MEDLINE and EMBASE for articles on drug therapy for primary Sjögren syndrome published between January 1, 1986, and April 30, 2010. Controlled trials of topical and systemic drugs including adult patients with primary Sjögren syndrome were selected as the primary information source. The search strategy yielded 37 trials. The authors reported that a placebo-controlled trial found significant improvement in the Schirmer and corneal staining scores, blurred vision, and artificial tear use in patients treated with topical ocular 0.05% cyclosporine. Three placebo-controlled trials found that pilocarpine was associated with improvements in dry mouth (61%-70% vs 24%-31% in the placebo group) and dry eye (42%-53% vs 26%). Two placebo-controlled trials found that cevimeline was associated with improvement in dry mouth (66%-76% vs 35%-37% in the placebo group) and dry eye (39%-72% vs 24%-30%). Small trials (<20 patients) found no significant improvement in sicca outcomes for oral prednisone or hydroxychloroquine and limited benefits for immunosuppressive agents (azathioprine and cyclosporine). A large trial found limited benefits for oral interferon alfa-2a. Two placebo-controlled trials of infliximab and etanercept did not achieve the primary outcome (a composite visual analog scale measuring joint pain, fatigue, and dryness); neither did 2 small trials (<30 patients) testing rituximab, although significant results were observed in some secondary outcomes and improvement compared with baseline. The authors concluded that, in primary Sjögren syndrome, evidence from controlled trials suggests benefits for pilocarpine and cevimeline for sicca features and topical cyclosporine for moderate or severe dry eye. Anti-tumor necrosis factor agents have not shown clinical efficacy, and larger controlled trials are needed to establish the efficacy of rituximab. An accompanying editorial by Vissink, et al. (2010) stated that "larger trials are needed before the role of rituximab in the treatment of primary Sjögren syndrome can be settled, not only with respect to its effect on salivary flow rate and xerostomia but also with regard to the effect of rituximab treatment on general symptoms, extraglandular involvement, and life-threatening situations in primary Sjögren syndrome."

Carubbi, et al. (2013) conducted a study to investigate the efficacy and safety of RTX in comparison to disease modifying anti-rheumatic drugs (DMARDs) in early active pSS patients. Forty-one patients with early pSS and active disease (EULAR Sjögren syndrome disease activity index, ESSDAI ≥ 6) were enrolled in the study. Patients were treated with either RTX or DMARDs in two different rheumatology centers and followed up for 120 weeks. Clinical assessment was performed by ESSDAI every 12 weeks up to week 120 and by self-reported global disease activity pain, sicca symptoms and fatigue on visual analogic scales, unstimulated saliva flow and Schirmer’s I test at week 12, 24, 48, 72, 96, and 120. Laboratory assessment was performed every 12 weeks to week 120. Two labial minor salivary gland (MSG) biopsies were obtained from all patients at the time of inclusion in the study and at week 120. The investigators concluded that their study demonstrated that RTX treatment results in a faster and more pronounced decrease of ESSDAI and other clinical parameters compared to DMARDs treatment. No adverse events were reported in the two groups. The investigators also observed that RTX is able to reduce glandular infiltrate, interfere with B/T compartmentalization and consequently
with the formation of ectopic lymphoid structures and germinal center-like structures in pSS-MSGs. The investigators reported that this is the first study performed in a large cohort of early active pSS patients for a period of 120 weeks. The investigators stated that the study showed that RTX is a safe and effective agent to be employed in pSS patients with systemic, extra-glandular involvement. Furthermore, they noted that their data on pSS-MSGs provide additional biological basis to employ RTX in this disease.

In a double-blind, randomized, placebo-controlled trial, Meijer et al (2010) examined the safety and effectiveness of rituximab in patients with primary Sjogren syndrome (pSS). Patients with active pSS, as determined by the revised American-European Consensus Group criteria, and a rate of stimulated whole saliva secretion of greater than or equal to 0.15 ml/min were treated with either rituximab (1,000 mg) or placebo infusions on days 1 and 15. Patients were assigned randomly to a treatment group in a ratio of 2:1 (rituximab:placebo). Follow-up was conducted at 5, 12, 24, 36, and 48 weeks. The primary end point was the stimulated whole saliva flow rate, while secondary end points included functional, laboratory, and subjective variables. A total of 30 patients with pSS (29 females) were randomly allocated to a treatment group. The mean +/- SD age of the patients receiving rituximab was 43 +/- 11 years and the disease duration was 63 +/- 50 months, while patients in the placebo group were age 43 +/- 17 years and had a disease duration of 67 +/- 63 months. In the rituximab group, significant improvements, in terms of the mean change from baseline compared with that in the placebo group, were found for the primary end point of the stimulated whole saliva flow rate (p = 0.038 versus placebo) and also for various laboratory parameters (B cell and rheumatoid factor [RF] levels), subjective parameters (Multidimensional Fatigue Inventory [MFI] scores and visual analog scale [VAS] scores for sicca symptoms), and extra-glandular manifestations. Moreover, in comparison with baseline values, rituximab treatment significantly improved the stimulated whole saliva flow rate (p = 0.004) and several other variables (e.g., B cell and RF levels, unstimulated whole saliva flow rate, lacrimal gland function on the lissamine green test, MFI scores, Short-Form 36 health survey scores, and VAS scores for sicca symptoms). One patient in the rituximab group developed mild serum sickness-like disease. The authors concluded that these results indicated that rituximab is an effective and safe treatment strategy for patients with pSS.

Mekinian et al (2012) evaluated RTX in pSS with peripheral nervous system (PNS) involvement. Patients with pSS and PNS involvement who were included in the French AIR registry were analyzed. A total of 17 patients (aged 60 years (44 to 78 years); 14 were female) were included in this analysis. Neurological improvement was noted in 11 patients (65 %) at 3 months. Rankin scale decreased from 3 (1 to 5) to 2 (1 to 5), 2 (1 to 5) and 2 (1 to 6) after 3, 6 and 9 months (p = 0.02). European Sjogren Syndrome Disease Activity Index (ESSDAI) decreased from 18 (10 to 44) to 11 (5 to 20), 11 (5 to 29) and 12 (5 to 30) after 3, 6 and 9 months (p < 0.05). Rituximab was effective in neurological involvement in 9/10 patients with vasculitis or cryoglobulinemia (90 %) (group 1) at 3 months and in 2/7 cases (29 %) without cryoglobulinemia and vasculitis (p = 0.03). Rankin and European Sjogren Syndrome Disease Activity Index scales decreased significantly in group 1. The authors concluded that RTX seems effective in cryoglobulinemia or vasculitis-related PNS involvement in pSS.

**Systemic Lupus Erythematosus and Lupus Nephritis**

Current evidence regarding the use of rituximab for systemic lupus erythematosus (SLE) is limited. A systematic evidence review and metaanalysis by Borba et al (2014) of biologic therapies for SLE found that rituximab showed no superiority over placebo in terms of efficacy, despite an acceptable safety profile.

In an open study, Leandro et al (2005) reported their findings of 24 patients with severe SLE treated with rituximab and followed for a minimum of 3 months. In the majority of patients (19 out of 24), 6 months follow-up data were described. The authors concluded that for patients who had failed conventional immunosuppressive therapy, considerable utility in the use of B-cell depletion has been demonstrated. They noted that the data obtained in this open study provided strong support for the
performance of a full double-blind control trial. This is in agreement with the observation of Sfikakis et al (2005) who stated that double-blind studies comparing rituximab with existing immunosuppressive therapies are needed.

Guidelines from the European League Against Rheumatism (EULAR, 2008) stated that in the absence of randomized controlled clinical trials, rituximab is recommended for selected patients with disease refractory to standard treatments with mycophenolate mofetil and cyclophosphamide. Established treatments for SLE include corticosteroids and the immunosuppressives cyclophosphamide and azathioprine. There is some evidence that oral mycophenolate may be an effective alternative to cyclophosphamide treatment in patients with lupus nephritis.

A study of rituximab for SLE (Ng et al, 2007) examined its efficacy in combination with cyclophosphamide and glucocorticoids in 90 patients with systemic lupus erythematosus refractory to conventional treatment. Following rituximab infusion patients were followed for from 3 to 40 months; a "meaningful" decrease in disease activity was noted in 80 %, infusions were well-tolerated in 90 % of patients, but adverse events (ascribed to hypersensitivity to the chimeric antibody) occurred in 10 %.

In December 2006, the FDA learned that 2 patients who were treated with rituximab for systemic lupus erythematosus developed progressive multifocal leukoencephalopathy (PML), a fatal viral infection of the central nervous system (FDA, 2007). This side effect has been reported in patients as late as 12 months after their last dose of rituximab. The FDA stated that SLE is not an approved indication for rituximab. A black box warning was added to the labeling of rituximab stating that JC virus infection resulting in PML and death has been reported in patients treated with rituximab.

Genentech, Inc. reported that the EXPLORER study, a phase II/III randomized, double-blind, placebo-controlled, multi-center study of rituximab for SLE, did not meet its primary endpoint defined as the proportion of rituximab treated patients who achieved a major clinical response or partial clinical response measured by BILAG, a lupus activity response index, compared to placebo at 52 weeks. A total of 257 patients were randomized 2:1 to receive rituximab plus prednisone or placebo plus prednisone in 2 infusions 15 days apart. Patients were retreated 6 months later with the same regimen. Patients were evaluated for efficacy every four weeks for 52 weeks. The majority of patients are being monitored to week 78. The study also did not meet any of the 6 secondary endpoints, including: time adjusted area-under-the-curve minus baseline of BILAG score over 52 weeks; proportion of patients who achieve a major clinical response, and proportion of patients who achieve a partial clinical response (including major clinical response) at week 52; proportion of patients who achieve BILAG C or better in all domains at week 24; time to moderate or severe flare over 52 weeks; change in SLE Expanded Health Survey physical function score from baseline at week 52; and proportion of subjects who achieve a major clinical response with 10 mg prednisone per day from weeks 24 to 52 (Genentech, 2008; Merrill, et al., 2010).

Rovin et al (2012) evaluated the efficacy and safety of rituximab in a randomized, double-blind, placebo-controlled phase III trial in patients with lupus nephritis treated concomitantly with mycophenolate mofetil (MMF) and corticosteroids. Patients (n = 144) with class III or class IV lupus nephritis were randomized 1:1 to receive rituximab (1,000 mg) or placebo on days 1, 15, 168, and 182. The primary end-point was renal response status at week 52. Rituximab depleted peripheral CD19+ cells in 71 of 72 patients. The overall (complete and partial) renal response rates were 45.8 % among the 72 patients receiving placebo and 56.9 % among the 72 patients receiving rituximab (p = 0.18); partial responses accounted for most of the difference. The primary end-point (superior response rate with rituximab) was not achieved. Eight placebo-treated patients and no rituximab-treated patients required cyclophosphamide rescue therapy through week 52. Statistically significant improvements in serum complement C3, C4, and anti-double-stranded DNA (anti-dsDNA) levels were observed among patients treated with rituximab. In both treatment groups, a reduction in anti-dsDNA levels greater than the median reduction was associated with reduced proteinuria. The rates of serious adverse events,
including infections, were similar in both groups. Neutropenia, leukopenia, and hypotension occurred more frequently in the rituximab group. The authors concluded that, although rituximab therapy led to more responders and greater reductions in anti-dsDNA and C3/C4 levels, it did not improve clinical outcomes after 1 year of treatment. The authors also found that the combination of rituximab with MMF and corticosteroids did not result in any new or unexpected safety signals.

For some patients with refractory LN, add-on rituximab may improve health outcomes. However, since SAEs were observed in lupus nephritis 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.

There is limited evidence for the use of rituximab as a last resort (third line) treatment of chronic cutaneous or musculoskeletal graft versus host disease. Available clinical trial evidence is limited to small, uncontrolled, phase II studies with limited follow-up. In addition, McIver et al (2010) also found that administration of rituximab early after T cell-deplete SCT is associated with prolonged profound and life-threatening cytopenias, and should be avoided.

The anti-CD20 monoclonal antibody rituximab produced a clinical response rate of 70 % mainly for musculoskeletal and cutaneous chronic GVHD (Cutler et al, 2006). These responses were durable through 1 year after initiation of therapy and allowed a 75 % reduction in steroid doses.

A review on immunosuppressive agents for graft versus host disease in UpToDate commented: “Prospective studies are investigating the use of the anti-CD20 monoclonal antibody, rituximab, in an attempt to decrease allogeneic donor B cell immunity and, potentially, associated chronic GVHD. While initial results demonstrate decreased B cell immunity and low rates of chronic GVHD, this approach remains experimental. Randomized trials are needed to determine the efficacy and toxicity of rituximab in this setting, including the effect on long-term B cell function.”

British Society of Haematology guidelines on acute graft versus host disease recommends against the use of rituximab. British Society of Haematology guidelines on chronic graft versus host disease suggest rituximab as a second line treatment option in refractory cutaneous or musculoskeletal chronic graft versus host disease. This is a weak recommendation based upon moderate quality evidence (2B).

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.

Current guidelines (Costanzo et al, 2010) recommend the use of rituximab for antibody mediated rejection in heart transplant recipients, with steroids, plasmapheresis and/or IVIG, to reduce the risk of recurrent rejection. Initial therapy of antibody-mediated rejection can include immunoabsorption and corticosteroid or plasmapheresis/low dose of IVIG and corticosteroid. The guidelines state that rituximab can be added to reduce the risk of recurrent rejection. Changes in therapy, which can be considered for maintenance immunosuppression in patients who experience antibody mediated rejection, can include switch to tacrolimus in patients receiving cyclosporine-based immunosuppression, increased doses of mycophenolate mofetil, and corticosteroids.

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.

**Autoimmune Mucocutaneous Blistering Diseases**

Rituximab has been increasingly used in autoimmune blistering dermatoses, mainly in pemphigus. Joly et al (2007) found that a single cycle of rituximab is an effective treatment for pemphigus vulgaris of pemphigus foliaceus. The investigators studied 21 patients with pemphigus vulgaris or pemphigus foliaceus whose disease had not responded to an 8-week course of 1.5 mg of prednisone per kilogram of body weight per day (corticosteroid-refractory disease), who had had at least 2 relapses despite doses of prednisone higher than 20 mg per day (corticosteroid-dependent disease), or who had severe contraindications to corticosteroids. Patients were treated with 4 weekly infusions of 375 mg of rituximab per square meter of body-surface area. Eighteen of 21 patients had a complete remission at 3 months after the end of treatment. In 8 of the 18 patients, this remission was maintained without corticosteroid or immunosuppressive therapy after a median follow-up of almost 3 years. One patient developed pyelonephritis and another died of septicemia. The investigators concluded that a single cycle of rituximab is an effective treatment for pemphigus (Joly et al, 2007). The investigators warned that, because of its potentially severe side effects, its use should be limited to the most severe types of the disease. An editorialist noted that this study demonstrated the value of a multi-center approach to accomplish relevant clinical research in orphan diseases such as pemphigus (Diaz, 2007).

Kasperkiewicz et al (2011) concluded that adjuvant rituximab is effective and well-tolerated not only in patients with pemphigus but also with pemphigoid. A total of 17 patients with refractory autoimmune blistering dermatoses (pemphigus vulgaris, n = 8; pemphigus foliaceus, n = 2; bullous pemphigoid, n = 2; mucous membrane pemphigoid, n = 5) were treated 4 times with rituximab at weekly or bi-weekly intervals. Six of 8 patients with a relapse after this regimen received rituximab again twice in a 2-week interval. The investigators reported that all lesions cleared in 14 patients (7 pemphigus vulgaris, 2 pemphigus foliaceus, 2 bullous pemphigoid, 3 mucous membrane pemphigoid), whereas partial healing
was found in 3 others (1 pemphigus vulgaris, 2 mucous membrane pemphigoid). Relapses occurred in 8 patients (5 pemphigus vulgaris, 2 pemphigus foliaceus, 1 bullous pemphigoid). Re-treatment with rituximab again resulted in complete (2 pemphigus vulgaris, 1 pemphigus foliaceus, 1 bullous pemphigoid) or partial (2 pemphigus vulgaris) remission.

Peterson and Chan (2009) performed a survey of 71 consecutive patients with autoimmune blistering diseases treated with rituximab from initial use up to 2007, using the PubMed database. The authors stated that a heterogeneous group of patients, including 51 patients with pemphigus vulgaris, 1 with pemphigus vegetans, 9 with pemphigus foliaceus, 5 with paraneoplastic pemphigus, 4 with epidermolysis bullosa acquisita, and 1 with both bullous pemphigoid and graft-versus-host disease was included in this survey. The authors reported that, overall, the monoclonal antibody seems to be effective in that 69% of patients showed complete response, 25% of patients showed partial response, whereas 6% of patients showed progressive disease. Six deaths occurred in association with the treatment, with 4 of these deaths in patients with paraneoplastic pemphigus, a disease characteristically resistant to conventional medication and with a high mortality rate.

Cavailhes et al (2009) note that epidermolysis bullosa acquisita (EBA) is a rare autoimmune sub-epidermal blistering disease; it is potentially serious and is often refractory to conventional treatments, including corticosteroids. The authors reported a new case of successful treatment of EBA using rituximab without relapse after 1 year of follow-up. A 76-year old man was seen for blisters of the skin and mucosa, atrophic scars and milia on areas of friction. The diagnosis of EBA was made on the basis of histological and immunohistochemical criteria. The patient was unsuccessfully treated with topical steroids, dapsone, topical tacrolimus, systemic steroids, mycophenolate mofetil, doxycycline and methotrexate. Four weekly infusions of rituximab of 375 mg/m(2) body area were performed, combined with systemic steroids: they proved beneficial within 3 weeks, with a noticeable improvement and no further blisters at 7 months. After 1 year of follow-up, the skin disease is still stable with 5 mg/day of prednisone alone being given. The authors concluded that this was the 8th reported case of treatment of EBA with rituximab and the 6th successful therapeutic outcome, with good steroid sparing effect and undeniable improvement in quality of life within several months and good tolerability at 12 months of follow-up. This treatment may be proposed early in cases of EBA refractory to conventional treatments. Moreover, the authors stated that clinical observation is necessary to study potential long-term adverse effects.

In a retrospective, comparative, interventional case series, Foster et al (2010) compared the safety and effectiveness of the combination therapy of rituximab (RTX) and intravenous immunoglobulin (IVIG) to other immunosuppressive regimens in the treatment of ocular cicatricial pemphigoid (OCP; n = 12). These investigators reviewed medical records of 12 patients with OCP. Ten of the 12 patients were blind in 1 eye after initial systemic immunosuppressive therapies (phase I treatment). Patients were then divided into 2 groups based on treatments received during phase II. The study group consisted of 6 patients who received the combination of RTX and IVIG during phase II of their treatment. For comparison purposes, the control group consisted of 6 patients who during phase II of their treatment received more aggressive immunosuppressive therapies, but not RTX and IVIG. Main outcome measures included blindness (best-corrected visual acuity [BCVA] less than or equal to 20/200) and OCP staging (Foster). The median total follow-up periods were 57.5 and 55.5 months in the control group and the study group, respectively. After phase I treatment, all 6 patients in the control group were blind in 1 eye. Similarly, 4 of the patients in the study group were blind in 1 eye, whereas 2 had good BCVA bilaterally but experienced persistent conjunctival inflammation despite phase I treatment. After phase II treatment, all 6 patients in the control group had OCP progression and became blind in both eyes. In contrast, BCVA was stable and no further progression of OCP staging was observed in all 6 patients in the study group. In the study group, the median follow-up from completion of the RTX and IVIG treatment protocol was 11 months. No adverse events, immediate or delayed, were reported in any of the patients who received the combination therapy of RTX and IVIG. The authors concluded that in this preliminary study, the combination therapy of RTX and IVIG arrested disease progression and prevented total blindness in patients with recalcitrant OCP. They noted that a larger cohort of patients needs to be studied before definitive conclusions can be made.
Lymphocyte-predominant Hodgkin's Lymphoma:

There are several published phase II studies of rituximab for lymphocyte predominance Hodgkin's disease (LPHD) (Younes et al, 2003; Ekstrand et al, 2003; Rehwald et al, 2003). Additional studies of rituximab for LPHD are currently ongoing. Younes et al (2003) examined the potential role of infiltrating benign B cells in classic HD lesions in supporting the survival of malignant Hodgkin and Reed-Sternberg (H/RS) cells. The authors initiated a pilot study of rituximab, which is used to primarily deplete normal B cells from HD lesions. Patients with recurrent, classic HD who had received a minimum of 2 prior treatment regimens, regardless of whether H/RS cells expressed CD20, were treated with 6 weekly doses of 375 mg/m2 rituximab to selectively deplete infiltrating benign B cells. Objective tumor response was determined 3 weeks after completion of the last dose of rituximab and every 3 months thereafter. Serum samples were collected from patients before they started rituximab therapy and 3 weeks after the final course of rituximab. Serum cytokine levels of interleukin 6 (IL-6), IL-10, IL-12, IL-13, and interferon gamma were determined using commercially available enzyme-linked immunosorbent assay kits. Twenty-two patients with nodular sclerosis histology were evaluable for treatment response. Five patients (22 %) achieved partial or complete remission that lasted for a median of 7.8 months (range of 3.3 to 14.9 months). Remissions were observed in patients only at lymph node and splenic sites, but not at extra-nodal sites, and were irrespective of CD20 expression by H/RS cells. Furthermore, systemic (B) symptoms resolved in 6 of 7 patients after therapy. In 2 patients, partial remissions were associated with a decline in serum IL-6 levels. The authors concluded that current data suggest that rituximab therapy in patients with recurrent, classic HD can alter serum IL-6 cytokine levels, can improve B symptoms, and may result in clinical remissions.

Ekstrand et al (2003) stated that LPHD is a unique clinical entity characterized by indolent nodal disease that tends to relapse after standard radiotherapy or chemotherapy. The malignant cells of LPHD are CD20+ and therefore rituximab may have activity with fewer late effects than standard therapy. In this phase 2 trial, 22 patients with CD20+ LPHD received 4 weekly doses of rituximab at 375 mg/m2. Ten patients had previously been treated for Hodgkin disease, while 12 patients had untreated disease. All 22 patients responded to rituximab (overall response rate, 100 %) with complete response (CR) in 9 (41 %), unconfirmed complete response in 1 (5 %), and partial response in 12 (54 %). Acute treatment-related adverse events were minimal. With a median follow-up of 13 months, 9 patients had relapsed, and estimated median freedom from progression was 10.2 months. Progressive disease was biopsied in 5 patients: 3 had recurrent LPHD, while 2 patients had transformation to large-cell non-Hodgkin lymphoma (LCL). All 3 patients with recurrent LPHD were retreated with rituximab, with a second CR seen in 1 patient and stable disease in 2. Rituximab induced prompt tumor reduction in each of 22 LPHD patients with minimal acute toxicity; however, based on the relatively short response duration seen in the trial and the concerns about transformation, rituximab should be considered investigational treatment for LPHD. Further clinical trials are needed to determine the optimal dosing schedule of rituximab, the potential for combination treatment, and the possible relationship of rituximab treatment to the development of LCL.

In a phase 2 study, Rehwald et al (2003) evaluated the safety and efficacy of rituximab in patients with relapsed LPHD or other CD20(+) subtypes of Hodgkin disease (HD). Eligibility criteria required expression of the CD20 antigen on more than 30 % of malignant cells. A total of 14 patients were treated with 4 weekly intravenous infusions of rituximab (375 mg/m2). All patients had at least 1 prior chemotherapy (median, 2). The median time from first diagnosis was 9 years. Adverse events, such
as rhinitis, fever, chills, and nausea, were usually transient and of mild to moderate grade, allowing outpatient treatment in most cases. All patients completed treatment and were eligible for a response. The overall response in 14 assessable patients was 86%, with 8 complete remissions and 4 partial remissions, and 2 patients with progressive disease. At a median follow-up of 12 months, 9 of 12 responders were in remission. The median duration of response has not been reached yet (20+ months). The authors concluded that rituximab is both safe and effective in a subgroup of CD20(+) patients with HD.

**Opsoclonus-myoclonus-ataxia**

Pranzatelli et al (2010) reported the findings of 12 immunotherapy-naïve children with opsoclonus-myoclonus syndrome (OMS) and cerebrospinal fluid (CSF) B cell expansion who received rituximab, adrenocorticotropic hormone (ACTH), and intravenous immunoglobulin. Motor severity lessened 73% by 6 months and 81% at 1 year (p < 0.0001). Opsoclonus and action myoclonus disappeared rapidly, whereas gait ataxia and some other motor components improved more slowly. Dosage of ACTH was tapered by 87%. Reduction in total CSF B cells was profound at 6 months (-93%). By study end, peripheral B cells returned to 53% of baseline and serum IgM levels to 63%. Overall clinical response trailed peripheral B cell and IgM depletion, but improvement continued after their levels recovered. All but 1 non-ambulatory subject became ambulatory without additional chemotherapy; 2 relapsed and remitted; 4 had rituximab-related or possibly related adverse events; and 2 had low-titer human anti-chimeric antibody. The authors concluded that combination of rituximab with conventional agents as initial therapy was effective and safe. They stated that a controlled trial with long-term safety monitoring is indicated.

Gorman et al (2010) stated that OMS is a severe autoimmune central nervous system disorder, which predominantly affects young children and causes lifelong neurological disability. Early recognition and treatment may yield better outcomes. Appreciation of the spectrum of clinical presentations of OMS, awareness of common mis-diagnoses, and utilization of diagnostic criteria may facilitate the timely diagnosis of OMS. Approximately 50% of patients have an associated neuroblastoma, which may escape detection by traditional methods and require MRI or computed tomography of the torso for diagnosis. In non-paraneoplastic cases, many associated infections have been reported. Although there has been progress in autoantibody identification and CSF B cell expansion is a common finding, there is no diagnostic biomarker for OMS currently. Approximately 80% of reported patients, typically treated with conventional therapies such as ACTH, corticosteroids, and/or intravenous immunoglobulin, develop long-term neurological morbidity. Newer treatment approaches using early, aggressive therapy with cyclophosphamide or rituximab are promising. The authors concluded that the diagnosis of OMS requires a high level of suspicion and a systematic approach for diagnostic testing, particularly for neuroblastoma. They stated that future collaborative studies are needed to determine if early, aggressive therapy will improve the typically poor long-term neurological outcome.

In a multi-center retrospective study, Dale et al (2014) evaluated the utility and safety of rituximab in pediatric autoimmune and inflammatory disorders of the CNS. A total of 144 children and adolescents (median age of 8 years, range of 0.7 to 17; 103 female) with NMDA receptor (NMDAR) encephalitis (n = 39), opsoclonus myoclonus ataxia syndrome (n = 32), neuromyelitis optica spectrum disorders (n = 20), neuropsychiatric systemic lupus erythematosus (n = 18), and other neuroinflammatory disorders (n = 35) were studied. Rituximab was given after a median duration of disease of 0.5 years (range of 0.05 to 9.5 years). Infusion adverse events were recorded in 18/144 (12.5%), including grade 4 (anaphylaxis) in 3. Eleven patients (7.6%) had an infectious adverse event (AE), including 2 with grade 5 (death) and 2 with grade 4 (disabling) infectious AE (median follow-up of 1.65 years [range of 0.1 to 8.5]). No patients developed progressive multifocal leukoencephalopathy. A definite, probable, or possible benefit was reported in 125 of 144 (87%) patients. A total of 17.4% of patients had a modified Rankin Scale (mRS) score of 0 to 2 at rituximab initiation, compared to 73.9% at outcome. The change in mRS 0 to 2 was greater in patients given rituximab early in their disease course compared to those treated later. The authors concluded that while limited by the retrospective nature of this analysis, these findings supported an off-label use of rituximab, although the significant risk of
infectious complications suggested rituximab should be restricted to disorders with significant morbidity and mortality. This study provides Class IV evidence that in pediatric autoimmune and inflammatory CNS disorders, rituximab improves neurologic outcomes with a 7.6% risk of adverse infections.

**Post-transplant lymphoproliferative disorder**

There is evidence for the effectiveness of rituximab for post-transplant lymphoproliferative disorders (PTLD) (Cincinnati Hospital Children's Medical Center, 2003). PTLD is a life-threatening complication following solid organ transplantation. Treatment with rituximab, a humanized anti-CD20 monoclonal antibody, has proved to be a promising approach and shown a low toxicity profile. Oertel et al (2005) reported on the results of a multi-center phase II trial investigating rituximab as single agent in 17 patients with PTLD. Transplanted organs were heart (n = 5), kidney (n = 4), lung (n = 4) and liver (n = 4). Patients were treated with 4 weekly doses of 375 mg/m² of rituximab. The mean follow-up time was 24.2 months. The investigators reported that rituximab therapy was well-tolerated and no severe adverse events were observed. The mean overall survival period is 37.0 months with 11 patients still living at the time of the report. In total, 9 patients (52.9%) achieved a complete remission, with a mean duration of 17.8 months. Partial remission was observed in 1 patient, minor remission in 2 patients, no change in 3 patients and 1 patient experienced progressive disease. Two patients relapsed, at intervals 3 and 5 months after obtaining complete remission. The investigators concluded that rituximab proved to be well-tolerated and effective in the treatment of PTLD.

**Relapsed or refractory hairy cell leukemia in persons who have failed at multiple (2 or more) courses of cladribine**

Rituximab may be considered for persons with relapsed or refractory hairy cell leukemia who have failed at least two courses of cladribine. The National Cancer Institute information on hairy cell leukemia (NCI, 2007) states that rituximab can be used for relapsed or refractory hairy cell leukemia after failure of purine analog therapy (i.e., cladribine). "Rituximab can induce durable complete remissions with minimal toxic effects in the majority of patients with relapsing or refractory disease after purine analog therapy. The lack of subsequent immunosuppression with rituximab has made this treatment the first choice among relapsing patients in the absence of a clinical trial." The largest clinical trial of rituximab for hairy cell leukemia reported to date (Nieva et al, 2003) reported that rituximab "has only modest single-agent activity in cladribine-failed HCL patients when compared with other agents active in this disease."

**Waldenström's macroglobulinemia**

National Comprehensive Cancer Network guidelines also include indications for rituximab in lymphocyte-predominant Hodgkin's lymphoma, and Waldenstrom's macroglobulinemia. The U.S. Pharmacopoeial Convention has concluded that rituximab is indicated for treatment of Waldenström's macroglobulinemia. Dimopolous et al (2002) reported on 27 patients with symptomatic Waldenström's macroglobulinemia who were treated with rituximab. Twelve patients (44%; 95% confidence interval [CI]: 25.5% to 64.7%) achieved a partial response after treatment with rituximab. Median time to response was 3.3 months (range of 2.2 to 7.1 months). The median time to progression for all patients was 16 months, and with a median follow-up of 15.7 months, 9 of 12 responding patients remain free of progression. The investigators reported that approximately 25% of patients experienced some mild form of infusion-related toxicity, usually fever and chills. The U.S. Pharmacopoeial Convention has also concluded that rituximab is indicated for treatment of idiopathic thrombocytopenic purpura. This conclusion is based on the results of several single-institution cohort studies that have reported on response rates exceeding 50%, and only minor adverse events. Stasi et al (2001) stated that "[i]n view of its mild toxicity and the lack of effective alternative treatments, its use in the setting of chronic refractory ITP is warranted."
References


Billing Coding/Physician Documentation Information

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<td>M05.00-M06.09</td>
<td>Rheumatoid arthritis code range</td>
</tr>
<tr>
<td>M06.80-M06.9</td>
<td></td>
</tr>
<tr>
<td>M30.0</td>
<td>Polyarteritis nodosa</td>
</tr>
<tr>
<td>M30.1</td>
<td>Polyarteritis with lung involvement (Churg-Strauss)</td>
</tr>
<tr>
<td>M31.1</td>
<td>Thrombotic microangiopathy</td>
</tr>
<tr>
<td>M31.30-M31.31</td>
<td>Wegener’s granulomatosis code range</td>
</tr>
<tr>
<td>M32.0-M32.9</td>
<td>Systemic lupus erythematosus code range (includes lupus nephritis)</td>
</tr>
<tr>
<td>M34.0-M34.9</td>
<td>Systemic sclerosis code range</td>
</tr>
<tr>
<td>M35.00-M35.09</td>
<td>Sicca syndrome (Sjogren)</td>
</tr>
<tr>
<td>N02.2</td>
<td>Recurrent and persistent hematuria with diffuse membranous glomerulonephritis</td>
</tr>
<tr>
<td>N05.2</td>
<td>Unspecified nephritic syndrome with diffuse membranous glomerulonephritis</td>
</tr>
<tr>
<td>N06.2</td>
<td>Isolated proteinuria with diffuse membranous glomerulonephritis</td>
</tr>
</tbody>
</table>

Additional Policy Key Words
Policy Number: 5.01.24

Policy Implementation/Update Information

05/2006  New policy titled Rituxan (rituximab)
05/2007  Reviewed – no changes made
05/2008  Reviewed – no changes made
05/2009  Reviewed – no changes made
05/2010  Revised – added Cimzia and Simponi to list of drugs patient may have inadequate response to before Rituxan is considered for coverage.
05/2011  Reviewed – no changes made
05/2012  Reviewed – no changes made
05/2013  Updated with new indication for Granulomatosis with Polyangitis (GPA) (Wegener’s Granulomatosis) and Microscopic Polyangitis (MPA)
05/2014  Policy reviewed – no changes made
09/2015 Updated with new indication for IgA vasculitis also known as Henoch-Schonlein purpura as medically necessary
05/2016  Policy reviewed-‘Idiopathic thrombocytopenic purpura in patients who do not respond to first-line treatments’ moved from medically necessary to investigational indication. Updated References
05/2017 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.
06/2017 Policy updated to include FDA-approved oncologic indications (NHL, CLL). Acute lymphoid leukemia (induction/consolidation therapy for Philadelphia chromosome-negative ALL for patients aged greater than or equal to 15 years), chronic lymphocytic leukemia/small lymphocytic lymphoma, Corticosteroid-refractory autoimmune blistering diseases (pemphigus vulgaris, pemphigus foliaceus, bullous pemphigoid, cicatricial pemphigoid, epidermolysis bullosa acquisita and paraneoplastic pemphigus), Immune
thrombocytopenic purpura (ITP), Multiple sclerosis (last resort treatment of relapsing disease not adequately responsive), Lymphocyte-predominant Hodgkin’s Lymphoma, refractory Opsoclonus-myoclonus-ataxia associated with neuroblastoma, Post-transplant lymphoproliferative disorder, Relapsed or refractory hairy cell leukemia, Sjogren syndrome refractory to corticosteroids and other immunosuppressive agents, and Waldenström’s macroglobulinemia were added to medical necessary (off-label indications) statement as detailed above.

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