Name of Policy: Non-Oncologic Uses of Rituximab (Rituxan)

Policy #: 044
Category: Medication/Drug
Latest Review Date: August 2014
Policy Grade: A

Background/Definitions:
As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

1. The technology must have final approval from the appropriate government regulatory bodies;
2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;
3. The technology must improve the net health outcome;
4. The technology must be as beneficial as any established alternatives;
5. The improvement must be attainable outside the investigational setting.

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. In accordance with generally accepted standards of medical practice; and
2. Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient’s illness, injury or disease; and
3. Not primarily for the convenience of the patient, physician or other health care provider; and
4. Not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient’s illness, injury or disease.
**Description of Procedure or Service:**
Rituximab is a monoclonal antibody against the CD20 antigen on B-lymphocytes. Rituximab reduces pre-B and B lymphocytes, and is successfully used to treat B-cell lymphoma. Over the last decade, rituximab has been used with increased frequency for non-oncologic indications, particularly autoimmune diseases that are thought to be B-cell mediated.

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

B cells are thought to play a role in the pathogenesis of rheumatoid arthritis (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.

Rituximab is administered by intravenous (IV) infusion. See Policy Guidelines for FDA-approved dosing regimens for RA and for Wegener granulomatosis (granulomatosis with polyangiitis [GPA]) and microscopic polyangiitis (MPA).

For oncologic uses of Rituximab, see MP #475- Uses of Monoclonal Antibodies for the Treatment of Non-Hodgkin Lymphoma, including Chronic Lymphocytic Leukemia, and Acute Myeloid Leukemia in the Non-Hematopoietic Stem-Cell Transplant Setting.

**Policy:**

**Effective for dates of service on or after September 1, 2014:**

**Labelled Indications**

**Rheumatoid Arthritis**

Rituximab for the treatment of adults with rheumatoid arthritis meets Blue Cross and Blue Shield of Alabama’s medical criteria for coverage under the following conditions:

- Rheumatoid arthritis is moderately- to severely-active (e.g., ≥8 swollen and ≥8 tender joints); AND
- Rituximab is administered in combination with methotrexate; AND
- Either:
  - Patient has had an inadequate response to 1 or more tumor necrosis factor (TNF) inhibitors; OR
  - 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 (e.g., due a recent [e.g., within 5 years] history of lymphoma or other malignancy; latent tuberculosis and contraindications to chemoprophylaxis; or previous demyelinating disease).
Granulomatosis with Polyangiitis (GPA) and Microscopic Polyangiitis (MPA)
Rituximab, in combination with glucocorticoids, meets Blue Cross and Blue Shield of Alabama’s medical criteria for the treatment of individuals with granulomatosis with polyangiitis (Wegener granulomatosis) and microscopic polyangiitis.

Off-Label Indications
Rituximab meets Blue Cross and Blue Shield of Alabama’s medical criteria for coverage for the following off-label indications:

- the following autoimmune hemolytic anemias (AIHA):
  - warm AIHA in corticosteroid-refractory patients;
  - cold agglutination syndrome;
- multicentric Castleman disease;
- cryoglobulinemic vasculitis
- refractory dermatomyositis
- Evans syndrome, refractory to immunosuppressive therapy
- factor inhibitors in patients with hemophilia who are refractory to conventional first-line treatments (eg, immune tolerance induction, corticosteroids with or without cyclophosphamide), preferably as add-on therapy
- steroid-refractory chronic graft-versus-host disease;
- desensitization of human leukocyte antigen (HLA)-sensitized renal transplant candidates before transplantation,
- idiopathic membranous nephropathy (IMN); when steroids and immunosuppressant drugs have been used and relapse of the disease occurs with the presence of proteinuria. (May include cases of glomerulonephritis that have met this same criteria)
- steroid-refractory idiopathic thrombocytopenic purpura;
- 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:
  - bullous pemphigoid;
  - mucous membrane pemphigoid, including ocular cicatrical pemphigoid; and
  - epidermolysis bullosa acquisita;
- pemphigus diseases (i.e., pemphigus vulgaris, pemphigus foliaceus, and paraneoplastic pemphigus) in treatment-refractory patients;
- primary Sjogren syndrome that is refractory to corticosteroids and other immunosuppressive agents;
- systemic lupus erythematosus (SLE)

Rituximab does not meet Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and is considered investigational for all other non-oncologic uses.

Effective for dates of service prior to September 1, 2014:
Rituximab meets Blue Cross and Blue Shield of Alabama’s medical criteria for coverage when used for the following non-oncologic diagnoses:
• Refractory immune thrombocytopenic purpura resistant to standard treatment such as; corticosteroids, IV immunoglobulin, cyclosporin, phosphoamide. Some may also have had splenectomy, this is not a prerequisite for coverage if Rituxan requested in this condition.
• Idiopathic membranous nephropathy (IMN); when steroids and immunosuppressant drugs have been used and relapse of the disease occurs with the presence of proteinuria. (May include cases of glomerulonephritis that have met this same criteria)
• Moderate-to-severe, active rheumatoid arthritis in adult patients in combination with methotrexate who have had an inadequate response to one or more TNF antagonist therapies
• Steroid refractory autoimmune hemolytic anemia (AIHA)
• Microscopic polyangiitis (MPA) in combination with corticosteroids
• Neuromyelitis optica
• Pemphigus
• Lupus
• Wegener’s granulomatosis (severe) refractory in combination with corticosteroids
• Evans syndrome, refractory to immunosuppressive therapy
• Graft-versus-host disease, chronic, steroid-refractory
• Cryoglobulinemic vasculitis
• Refractory dermatomyositis

Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the member's contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:
FDA-Approved Uses
Rheumatoid Arthritis (RA)
Rituximab is FDA-approved in combination with methotrexate (MTX) to reduce signs and symptoms of moderately- to severely-active RA in adults who have had an inadequate response to at least one tumor necrosis factor (TNF)-inhibitor. Use in patients with RA who have not had a previous inadequate response to one or more TNF inhibitor is not recommended.

FDA-approval of rituximab for RA was based on 4 placebo-controlled, randomized trials. Three trials enrolled adults (≥18 years of age) with moderately- to severely-active RA (defined as ≥8 swollen and ≥8 tender joints) who had a previous inadequate response to at least one TNF inhibitor. In the REFLEX trial, patients who received a single course of rituximab with concomitant MTX had statistically significant and clinically meaningful improvements in disease activity at 24 weeks (as assessed by 20%, 50%, and 70% improvements in American College of Rheumatology [ACR] response criteria [ACR20, ACR50, and ACR70, respectively]) compared
with patients who received placebo. On radiographic examination, progression of joint space narrowing and erosion at 48 and 96 weeks was less in patients who received rituximab: At 48 weeks, 60% of rituximab-treated patients had no progression of structural damage compared with 46% of placebo-treated patients; 87% of rituximab-treated patients who had no progression at 48 weeks also had no progression at 96 weeks. In the SUNRISE trial, patients who received two courses of rituximab approximately six months apart had improved outcomes at 48 weeks (as assessed by ACR20) compared with those who received only one course of rituximab. A third trial showed statistically significant and clinically meaningful improvements in physical function at 24 and 48 weeks in patients who received an initial course of 500 mg or 1000 mg rituximab compared with patients who received placebo. Radiographic responses were not assessed.

A fourth randomized controlled trial (RCT) (IMAGE) compared rituximab 500 mg with 1000 mg dosing in MTX-naive patients. All patients received methotrexate. Patients who had active disease at 24 weeks could receive another course of rituximab at their assigned dose. At 48 weeks, the proportion of patients achieving clinically meaningful responses (ACR20, ACR50, and ACR70) was similar in both rituximab groups and greater than placebo. However, compared with placebo, a statistically significant (67%) reduction in joint space narrowing and erosion was observed in the rituximab 1000-mg group only.

Other studies have confirmed improvements in ACR20, ACR50, and ACR70 in patients treated with rituximab plus methotrexate compared with placebo plus methotrexate (summarized by Thaler et al (2012)). Keystone et al (2012) reported five-year follow-up of the pivotal REFLEX trial. Patients initially randomized to the placebo arm could receive rituximab in an observational extension study. In 400 patients who received 1 course of rituximab, ACR20, ACR50, and ACR70 responses were 62%, 31%, and 13%, respectively. In 91 patients who received five courses of rituximab, responses were 70%, 42%, and 22%, respectively. In 184 patients who had baseline and five-year radiographs available, progression of joint damage over five years was less in rituximab-treated than in placebo-treated patients, although this difference was not statistically significant. Adverse events rates were generally stable over five years of follow-up.

Section Summary
Four RCTs established the efficacy of rituximab in combination with methotrexate (MTX) for patients with RA who had an inadequate response to 1 or more tumor necrosis factor (TNF) inhibitors. Subsequent publications have confirmed this finding. A five-year extension study reported sustained improvements in clinical and radiographic outcomes in patients who received at least one 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 methotrexate and contraindications to TNF inhibitor therapy, rituximab may be a reasonable option. In the five-year extension study, adverse event rates were generally stable over time.

Wegener Granulomatosis (Granulomatosis with Polyangiitis [GPA]) and Microscopic Polyangiitis (MPA)
Wegener granulomatosis (GPA), MPA, and Churg-Strauss syndrome are classified as antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides because most patients with
generalized disease have antibodies against proteinase 3 (PR3) or myeloperoxidase (MPO), enzymes found in neutrophil granulocytes. Each vasculitis can be distinguished by the predominant type of immunofluorescence staining pattern (antibody) present, e.g., cytoplasmic ANCA (anti-PR3) in GPA and perinuclear ANCA (anti-MPO) in MPA. These vasculitides also are considered pauci-immune because, unlike immune-complex vasculitides, they are not characterized by immune complex deposition. ANCA-associated vasculitides affect small-to-medium-size blood vessels, particularly in the respiratory tract and kidneys; the characteristic kidney lesion is pauci-immune focal and segmental necrotizing and crescentic glomerulonephritis. Limited vasculitis may respond to MTX plus corticosteroids; standard treatment for more severe disease is cyclophosphamide plus corticosteroids.

Rituximab is FDA-approved in combination with corticosteroids for the treatment of adults with GPA and MPA. FDA-approval of rituximab for GPA and MPA was based on one active-controlled, RCT, the Rituximab in ANCA-Associated Vasculitis (RAVE) noninferiority trial. Patients 15 years of age or older who had severe (Birmingham Vasculitis Activity Score for Granulomatosis with Polyangiitis [BVAS/GPA] ≥3 [scores range from 0 to 63 with higher scores indicating more active disease], with at least one major item) GPA (n=151) or MPA (n=48) were enrolled. Patients with Churg-Strauss syndrome, considered by the authors to be a mimicker of ANCA-associated vasculitis, were excluded. Patients with severe alveolar hemorrhage or severe kidney disease (serum creatinine >4 mg/dL) also were excluded. Approximately half of patients had newly diagnosed disease and half had relapsing disease, with mean disease duration of approximately six years. Patients were randomized to receive rituximab 375 mg/m² weekly for four weeks (remission induction phase) followed by oral placebo beginning at three to six months (maintenance phase; n=99), or cyclophosphamide 2 mg/kg orally daily for three to six months (remission induction) followed by oral azathioprine daily beginning at three to six months (maintenance phase; n=98). All patients received one to three pulse doses of parenteral methylprednisolone 1000 mg followed by prednisone 1mg/kg orally daily. Patients who achieved remission tapered and discontinued prednisone by month five. The primary end point was complete remission at six months, defined as BVAS/GPA of ‘0’ off prednisone. The prespecified non-inferiority margin was a treatment difference of –20 percentage points (rituximab group minus cyclophosphamide group). At six months, 63% of patients in the rituximab group and 52% of patients in the cyclophosphamide group achieved complete remission, for a treatment difference of 11 percentage points (95% confidence interval [CI], –3 to 24), which exceeded the noninferiority margin. The incidence of adverse events was similar between treatment groups, with Grade 2 or higher leukopenia more common in the cyclophosphamide group (10% vs 3% rituximab) and hospitalizations due to disease or treatment more common in the rituximab (8% vs 2% cyclophosphamide).

Specks et al (2013) published 18-month follow-up results. Patient blinding was maintained throughout the follow-up period. Among rituximab-treated patients, 47% achieved and maintained complete remission to 12 months, and 39% maintained complete remission to 18 months. In the cyclophosphamide (azathioprine) group, 38% achieved and maintained complete remission to12 months, and 32% maintained complete remission to 18 months. Treatment differences at 12 and 18 months (9 percentage points [95% CI, –5 to 22] at 12 months and 7 percentage points [95% CI, –7 to 20] at 18 months) exceeded the noninferiority threshold (–20 percentage points) but not the superiority threshold (0).
Jones et al (2021) conducted an open-label RCT (RITUXVAS) to compare first-line induction regimens in 44 patients who had newly diagnosed ANCA-associated vasculitis with renal involvement (50% GPA, 36% MPA, 14% renal-limited vasculitis). Renal involvement was defined as necrotizing glomerulonephritis on biopsy, or red-cell casts or hematuria (≥30 red cells per high-power field) on urinalysis. Median baseline glomerular filtration rate (GFR) was 18 mL/min; nine patients were dialysis-dependent (GFR=0). Patients were randomized 3:1 to rituximab 375 mg/m² weekly for four weeks plus intravenous (IV) cyclophosphamide 15 mg/kg with the first and third rituximab infusions, or IV cyclophosphamide for three to six months followed by azathioprine. Both groups received one dose of methylprednisolone 1g IV and oral corticosteroid 1mg/kg daily reducing to 5mg daily at the end of six months. Primary outcomes were sustained remission (BVAS of 0 for ≥6 months) and incidence of severe adverse events at 12 months. No patients were lost to follow-up. At 12 months, between-group differences in primary outcomes were not statistically significant. Twenty-five patients in the rituximab group (76%) and nine patients in the control group (82%) had a sustained remission (chi-square, p=0.68). Severe adverse events occurred in 14 patients in the rituximab group (42%) and four patients in the control group (36%; chi-square, p=0.77); two patients in the rituximab group (6%) and no patients in the control group developed cancer (malignant melanoma and breast cancer). Among secondary outcomes, median time to remission was 90 days (interquartile range [IQR], 79-112) in the rituximab group and 94 days (IQR, 91 to 100) in the control group (log-rank test, p=0.87). At 12 months, median increase from baseline GFR was 19 mL/min in the rituximab group and 15 mL/min in the control group (analysis of covariance [ANCOVA], p=0.14). Six of eight dialysis-dependent patients randomized to rituximab had a sustained remission, five of whom no longer required dialysis; one dialysis-dependent randomized to control died soon after study entry. Eighteen percent of patients in each group had serious infections, and 18% in each group died. At 24 months, six (18%) of 33 patients in the rituximab group and three (27%) of 11 patients in the control group (27%) had died.

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

Off-Label Uses
Autoimmune Blood Disorders
Autoimmune Hemolytic Anemia (AIHA)
AIHA comprises direct Coombs-positive anemias, such as warm (80% of AIHA) and cold autoantibody types, and drug-induced AIHA. Warm AIHA is mediated by warm-reactive antibodies, primarily immunoglobulin G (IgG), that react optimally with human red blood cells
in vitro at 37 degrees Celsius (98.6 degrees Fahrenheit). Cold-reactive antibodies, primarily IgM, react maximally at 4º degrees Celsius (39 degrees Fahrenheit). Cold AIHA in turn comprises cold agglutinin syndrome and paroxysmal cold hemoglobinuria. Warm and cold AIHA may be idiopathic (primary) or secondary, e.g., to lymphoma or lymphoproliferative disorders. Corticosteroids are first-line treatment in warm AIHA but less effective in cold AIHA.

A 2011 systematic review of treatments for idiopathic warm AIHA in adults identified three studies (case series) of rituximab treatment for refractory disease (total N=42). Overall response rate was 93% (complete response [CR], 43%; partial response [PR], 50%). One study reported relapse in two (15%) of 13 responders and severe sepsis in one (4%) of 27 rituximab-treated patients with a mean follow-up of 21 months. The authors of the systematic review recommended rituximab 375 mg/m² weekly for four weeks or splenectomy for relapsed or refractory warm AIHA (Level 2 recommendation [evidence suggests that benefits and risks are finely balanced or uncertain] based on level C evidence [case series]).

Subsequently, Birgens et al (2013) published a multicenter RCT of first-line rituximab in newly-diagnosed patients with idiopathic or secondary warm AIHA. Patients were randomized to rituximab (375 mg/m² weekly for four weeks) plus short-course (two weeks followed by taper) prednisolone (n=32) or prednisolone alone (n=32). At 12 months, overall response rate was 75% in the rituximab group and 36% in the control group (chi-square, p=0.003). At 36 months, 70% of rituximab responders and 45% of control responders maintained complete or partial response (log-rank, p=0.02). Serious adverse events occurred in nine (28%) of 32 rituximab-treated patients and five (17%) of 32 controls (Fisher’s exact test, p=0.12). These included five serious infections in the rituximab group and two serious infections in controls (Fisher’s exact test, p=0.16).

In a 2008 review of cold AIHA, Petz identified 11 case reports and case series of rituximab in cold agglutinin syndrome (CAS). In two case series (total N=47), overall response rate was 62%. Median duration of response in 20 responders was 11 months, and no serious adverse events were reported in 20 rituximab-treated patients. Based on this evidence, Petz suggested rituximab as a treatment option for CAS, along with avoidance of cold and immunosuppressive drugs. Due to the generally self-limiting course and excellent prognosis of paroxysmal cold hemoglobinuria, rituximab is not considered a treatment option.

**Idiopathic Thrombocytopenic Purpura (ITP)**

ITP is an acquired autoimmune disorder with no known cause, although it can co-occur with other autoimmune diseases. Corticosteroids are standard initial treatment. However, relapses are common within the first year, and splenectomy is often required. Rituximab has been investigated to delay or avoid splenectomy.

Auger et al (2012) conducted a systematic review with meta-analysis of studies evaluating rituximab before splenectomy in adults with ITP. Literature was searched through May 2011; 15 retrospective or prospective observational studies and four RCTs were included (total N=368 non-splenectomized patients). Publication bias was not detected. Thirteen studies dosed rituximab at 375 mg/m² weekly for four weeks; six studies used alternative regimens. Concomitant medications were not described. Median follow-up was nine months (range, 2.3-
Pooled overall response rate (platelet count $>50 \times 10^9/L$) was 57% (95% CI, 48 to 65; $I^2=49\%$), and 57% (95% CI, 35 to 76; $I^2=79\%$) at one year. In separate analyses, CR rate (defined as platelet count either $>150 \times 10^9/L$ or $>100 \times 10^9/L$) was 41% (95% CI, 33 to 50; $I^2=51\%$) and 40% (95% CI, 31 to 49; $I^2=0\%$) at one year. In 36 responding patients, mean time to response and median duration of response were 6.3 weeks (95% CI, 2.8 to 9.9) and 49 weeks (range, 17-60), respectively. Adverse events and meta-analysis of RCT control arms were not reported.

Liang et al (2012) conducted a systematic review with meta-analysis of studies of rituximab for ITP in children. Literature was searched through December 2011, and 30 case series or case reports were included (total N=370). Publication bias was not detected. Median patient age was approximately eight years (range, 6 months to 19 years). Thirty-nine patients (11%) were splenectomized. The most common rituximab dose (in 47% of patients) was 375 mg/m$^2$ weekly for four doses; concomitant medications were not described. Pooled overall response rate (platelet count $\geq 30 \times 10^9/L$ with at least doubling of the platelet count, a standard response criterion) was 68% (95% CI, 58 to 77; $I^2=68\%$), and pooled CR (platelet count $\geq 100 \times 10^9/L$) was 39% (95% CI, 30 to 49; $I^2=57\%$). Median time to response was 3.0 weeks (IQR, 1.0-3.6) in 40 responders, and median duration of response was 12.8 months (IQR, 4.5 to 25.1). Incidence of Grade 3-4 infection and Grade 3-4 immediate hypersensitivity reaction or serum sickness was 4% each.

Two RCTs published after these systematic reviews examined rituximab in adult patients with newly-diagnosed ITP. Gudbrandsdottir et al (2013) randomized 133 patients with newly-diagnosed ITP to rituximab 375 mg/m$^2$ weekly for four weeks plus dexamethasone 40 mg daily for four days (n=62) or dexamethasone alone (n=72). Patients had baseline platelets counts of $25 \times 10^9/L$ or less, or $50 \times 10^9/L$ or less with bleeding symptoms. Median follow-up was 2.5 years. Overall response rate (platelets count $\geq 50 \times 10^9/L$) sustained at six months was 58% in the rituximab group and 37% in the control group (Fisher’s exact test, p=0.02); at 12 months, sustained response rate was 53% and 33%, respectively (Fisher’s exact test, P<0.05). Among responders, median time to rescue treatment was not reached in the rituximab group and 7.4 months in the control group (log-rank test, p=0.007). Median platelet count at time of rescue treatment was $15 \times 10^9/L$ (IQR, 7-24). Time to relapse also was longer in the rituximab group (log-rank test, p=0.03). Serious adverse events occurred more commonly in the rituximab group than in the control group (26% vs 11%; Fisher’s exact test, p=0.04). Because the authors reported numbers of adverse events rather than patients who experienced adverse events, incidences could not be calculated.

Arnold et al (2012) reported on a feasibility study of rituximab in nonsplenectomized adults with newly-diagnosed (47%) or relapsed (53%) ITP. Sixty patients were randomized to rituximab 375 mg/m two weekly for four weeks (n=33) or placebo (n=27), both administered in combination with standard treatments (most commonly prednisone, dexamethasone, and IVIG). The primary efficacy outcome was a composite of any platelet count less than $50 \times 10^9/L$, significant bleeding, or rescue treatment once standard treatment was stopped. At six months, the between-group difference of the composite end point was not statistically significant (64% rituximab vs 78% placebo; relative risk [RR], 0.81 [95% CI, 0.59 to 1.11]). Differences in overall (platelet count $\geq 30 \times 10^9/L$) or complete (platelet count $\geq 100 \times 10^9/L$) response were not
statistically significant at six or 12 months. Significant bleeding events occurred less commonly in the rituximab group than in the control group (25% vs 35%). The number of infections (any grade) and serious adverse events were comparable between groups. Because numbers of adverse events rather than patients who experienced adverse events were reported, incidences could not be calculated.

**Thrombotic Thrombocytopenic Purpura (TTP)**
TTP is a life-threatening condition characterized by microvascular thrombosis, thrombocytopenia and microangiopathic hemolytic anemia leading to end-organ ischemia and infarction (commonly brain, heart, and kidneys). TTP is due to an acquired (95% of cases) or congenital (5% of cases) deficiency of the von Willebrand factor (VWF)-cleaving protease, ADAMTS13. In 38%-95% of cases of idiopathic TTP, anti-ADAMTS13 neutralizing antibodies are present. When ADAMTS13 is absent or depleted, large uncleaved VWF multimers aggregate in high shear areas of the microvasculature, leading to thrombotic microangiopathy (TMA). The mainstay of treatment for TTP is plasma exchange and corticosteroids. Refractory TTP, defined as progression of clinical symptoms during plasma exchange therapy, occurs in 10%-20% of acquired TTP cases. For these patients, increased plasma exchange and/or addition of cyclosporine are current treatment options.

**Relapsed Or Refractory TTP**
Scully et al (2011) conducted a Phase 2, multicenter, cohort study in England. Forty patients with anti-ADAMTS13 antibody-positive, new-onset (85%) or acute relapsed (15%) TTP were enrolled and compared with an age-, sex- and ethnicity-matched historical control group of 40 patients. Enrolled patients received rituximab 375 mg/m² weekly for four weeks (protocol maximum of eight infusions); three patients died and one withdrew before receiving all four doses of rituximab. All patients and historical controls received plasma exchange at admission and then daily (or twice daily for new or progressive neurologic or cardiac symptoms) until remission, defined as sustained platelet count (>150×10⁹/L) for two consecutive days; corticosteroid (typically methylprednisolone 1 g IV daily) was given for three days. The primary efficacy outcome was the number of plasma exchange treatments to remission. Forty enrolled patients received a median of 16.5 (range, 4-34) plasma exchange treatments compared with 18 (range, 6-92) treatments in the historical control group (Mann Whitney test, p=0.5). Among secondary outcomes, there was no statistical difference between groups in the number of hospital admission days, but among patients who relapsed (four in the rituximab group and 21 in the control group), median time to relapse (defined as readmission with thrombocytopenia <150×10⁹/L 30 days after discharge from an acute episode) was longer in rituximab-treated patients than in historical controls (27 months [range, 17-31] vs 18 months [range, 3-60]). However, follow-up for rituximab and control groups was 12 and 49 months, respectively.

In 2007, Scully et al reported a multicenter cohort study of 25 patients who had anti-ADAMTS13 antibody-positive acute relapsing (56%) or acute refractory (44%) TTP. Patients received methylprednisolone daily for three days, daily plasma exchange until sustained platelet count (defined as above), and rituximab 375 mg/m² immediately after plasma exchange weekly for four weeks. All 25 patients achieved clinical remission (defined as cessation of plasma exchange, sustained platelet count, and absence of clinical disease) within one to three weeks of treatment. During median follow-up of 10 months (range, 1-33), there were no relapses.
This study was one of 15 case series and 16 case reports (total N=100) included in a systematic review by Tun et al (2012) of immune-mediated, relapsed or refractory TTP treated with rituximab. Studies of secondary TTP and empirical rituximab treatment were excluded. In all studies, rituximab was dosed at 375 mg/m² weekly for a median of four doses (range, 1-8). Ninety-eight patients (98%) achieved CR, defined as platelet recovery, lack of TTP-related symptoms, and no evidence of microangiopathic hemolytic anemia lasting more than 30 days. Two patients (2%) were considered nonresponders. During median follow-up of 13 months (range, 1-97), 9% of patients who achieved CR relapsed. Anti-ADAMTS13 antibody positivity and severe ADAMTS13 deficiency (enzyme activity <10%) predicted response to rituximab (positive predictive value, 99% for both). Serious rituximab-related adverse events occurred in three patients: acute biventricular cardiogenic shock, sacral abscess, and abdominal abscess.

**TTP Prophylaxis**

Fakhouri et al (2005) reported on five patients with highly recurrent (4 to 15 episodes) TTP who were not experiencing an acute TTP relapse. Patients received prophylactic rituximab 375 mg/m² weekly for four weeks. Although patients were in clinical remission, all had undetectable ADAMTS13 activity, suggesting susceptibility to relapse. At three, six, and nine months, 80%, 100%, and 80% achieved clinical remission, defined antibody.

**Section summary**

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 a randomized controlled trial enrolled patients with previously untreated disease. Response rates were 75%-93%; sustained responses to three years were observed; relapses occurred in 5%-15% of patients. Serious infections were observed in 4%-15% of patients. For cold agglutination syndrome (CAS), which generally has a poorer response than warm AIHA to first-line corticosteroids, a response rate of 62% was reported. As a potential corticosteroid-sparing agent in warm AIHA and effective treatment for CAS, rituximab may improve health outcomes. Rituximab is not considered a treatment option for paroxysmal cold hemoglobinuria.

Rituximab is being studied as a splenectomy-delaying or -avoiding approach in patients with ITP. Two systematic reviews of primarily observational studies (1 in children [median age, eight years] and one in adults) and two RCTs in adults investigated mostly non-splenectomized patients. Overall and complete response rates were approximately 57% and 40%, respectively, in adults, and 68% and 39% in children. Median response durations were approximately one year. One RCT of newly-diagnosed patients reported an improved overall response rate with rituximab in combination with corticosteroid compared with corticosteroid alone, but another did not. Adverse event reporting was inconsistent; serious infections and hypersensitivity reactions occurred in 4% of 370 children included in the systematic review. Overall, evidence suggests potentially improved health outcomes in patients with steroid-refractory ITP who are able to delay or avoid splenectomy with rituximab treatment.

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, evidence comprised case series and case reports, summarized in a systematic review that reported remission in 98% of rituximab-treated patients with a median follow-up of 10 months. A case series of five patients with recurrent TTP in remission who received prophylactic rituximab reported maintenance of remission in four patients at nine months.

This evidence suggests that further study of rituximab in patients with relapsed and refractory TTP is warranted. However, improved health outcomes have not been shown. Rituximab has rare but potentially fatal adverse effects. Although TTP also is considered life-threatening, knowledge about the balance of risks and benefits of rituximab in the acute or prophylactic setting is currently lacking.

**Factor Inhibitors in Hemophilia**

Hemophilia is a coagulopathy characterized by reduced, absent, or non-functioning clotting factor VIII (hemophilia A) or, less commonly, factor IX (hemophilia B). Treatment comprises replacement therapy with the missing or deficient clotting factor. Over time, antibodies to infused clotting factor develop in 20%-30% of patients with severe hemophilia A and 2%-5% of patients with hemophilia B. If left untreated, antibody inhibitors eventually render replacement therapy ineffective. Immune tolerance induction (ITI) is recommended first-line treatment of factor inhibitors in hemophilia. ITI comprises increasing the dose and frequency of factor infusions until inhibitor is undetectable and FVIII levels normalize. Success rate is low (25%), and associated risks (e.g., anaphylaxis, irreversible nephrotic syndrome) are significant. Other regimens incorporate immunosuppressive drugs. Rituximab has been investigated as an alternative to ITI or for patients who are nonresponsive to ITI.

Hemophilia is generally considered a genetic disorder, but acquired hemophilia A is a rare autoimmune disease caused by acquired autoantibodies against factor VIII. Underlying medical conditions, such as autoimmune diseases, solid tumors, lymphoproliferative malignancies, or pregnancy, can be identified in approximately half of patients. Immunosuppressive therapy with corticosteroids alone or in combination with cyclophosphamide is recommended for first-line inhibitor eradication. Rituximab has been studied as second-line treatment in this setting.

**Congenital Hemophilia**

Collins et al (2013) reviewed the literature on rituximab for treatment of factor inhibitors in congenital hemophilia. Several case reports in patients who failed conventional ITI reported mixed responses. A cohort study of 15 patients refractory to first-line ITI showed improved response when rituximab was added to ITI rather used as monotherapy. In case reports and case series, rituximab has been added to ITI in patients with hemophilia B with mixed results.

In 2008, Franchini et al published a systematic review of rituximab in congenital hemophilia with inhibitors. A literature search identified 29 studies (case reports and case series; total N=49). In most reports, rituximab was given after failure of several courses of conventional ITI. Half of studies administered rituximab in combination with ITI or other immunosuppressive treatment (e.g., plasmapheresis, immunoadsorption, immunosuppressive drugs), and half...
administered rituximab monotherapy. Analysis of individual patient data showed complete remission in 53% of patients. No serious rituximab-related adverse events were reported. In multivariate analysis, coadministration with factor VIII ITI was statistically associated with response (HR, 4.7 [95% CI, 1.6 to 13.7]; p=0.005), although the confidence interval was wide suggesting instability of the effect estimate, likely due to small numbers.

**Acquired Hemophilia A**
Huth-Kühne et al (2009) reviewed the literature on rituximab for inhibitor eradication in acquired hemophilia A. Uncontrolled studies and case reports usually administered rituximab in combination with other immunosuppressive treatments. Remission rates in 43 rituximab-treated patients (half first-line therapy, half second-line therapy) and 44 control patients who were treated with cyclophosphamide and corticosteroids (all first-line) were comparable. A registry study reported response rates of 42% with rituximab monotherapy, 64% with rituximab combination therapy, and 70% with cyclophosphamide plus corticosteroids. Incidence of adverse events was similar across treatment arms.

Section Summary: Rituximab for factor inhibitor eradication in congenital hemophilia and acquired hemophilia A has been studied in a small number of patients, primarily in case reports and cohort studies. In immune tolerance induction (ITI)-refractory patients with congenital hemophilia and factor inhibitor, complete remission occurred in 53% of patients who received rituximab alone or in combination with continued ITI; a small cohort study supported combination therapy in the refractory setting. A comparative study in acquired hemophilia A did not find improved response rates in patients treated with rituximab alone or in combination compared with standard cyclophosphamide plus cyclosporine. Evidence does not support rituximab as an alternative to standard treatments for factor inhibitor eradication (i.e., 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 adverse events. 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 (HCV)-Associated Cryoglobulinemic Vasculitis**
Of three types of cryoglobulinemia, Type 2 and Type 3 may be called “mixed” due to the clonal expansion of more than one immunoglobulin class, commonly IgM and IgG. (Type 1 in contrast is characterized by a single monoclonal immunoglobulin.) Eighty percent of mixed cryoglobulinemic vasculitis is associated with chronic HCV infection. Treatment of the underlying infection to achieve sustained viral response (SVR) is the treatment of choice. For patients who do not achieve SVR, corticosteroids and cytotoxic agents are alternative treatment options, but may exacerbate underlying liver disease.

In 2013, Dammacco et al and Puéchal et al published reviews of HCV-associated cryoglobulinemic vasculitis. Previous treatment recommendations, recently-published RCTs and heterogeneous nonrandomized studies (that varied in design, HCV genotype, previous treatment, rituximab dose, and concomitant therapy) (total N=377 patients) reported response rates of approximately 80%, and led the reviewers to draw the following conclusions:
• The choice of most suitable treatment for a given patient is based on the level of disease activity and the extent and severity of organ involvement.
  o For patients with mild-to moderate disease activity, antiviral therapy is recommended as first-line treatment.
  o For patients with active disease that is resistant to antiviral agents, and for patients with severe (e.g., leg ulcers, glomerulonephritis, peripheral neuropathy) or life-threatening cryoglobulinemic vasculitis, the addition of rituximab (or other B-cell-depleting monoclonal antibody) may slow or halt disease progression.
  o Peginterferon alfa may exacerbate some clinical features of cryoglobulinemic vasculitis, such as skin ulcers and peripheral neuropathy.
  o When rituximab is added, plasmapheresis and immunosuppressive therapy also should be added.

• Optimal rituximab dosing for vasculitis has not been determined. Most patients in studies received four weekly infusions of 375 mg/m².
  o One-gram dosing of rituximab may precipitate cryoglobulin and rituximab.

• HCV load, which does not appear to be associated with detectable adverse effects on the liver or with HCV reactivation, may increase during rituximab therapy.

• Viral load and liver function tests should be monitored at regular intervals during rituximab treatment.

Section Summary
Recent reviews summarized the literature for rituximab to treat hepatitis C virus (HCV)-associated cryoglobulinemic vasculitis. Across two 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 peginterferon-free drug regimens. More effective antiviral treatments should improve outcomes, eg, virologic and immunologic responses and cure rate of both HCV and associated vasculitis. However, for patients with antiviral-resistant active disease or with severe or life-threatening cryoglobulinemic vasculitis, rituximab in combination with current treatments may improve health outcomes. Viral load and liver function tests should be monitored during rituximab treatment.

Mixed Connective Tissue Disease (MCTD)
MCTD has mixed features of systemic lupus erythematosus (SLE), systemic sclerosis (SSc), polymyositis/dermatomyositis (PM/DM), and RA in the presence of increased anti-ribonucleoprotein (anti-RNP) antibodies. Although some question whether MCTD is a distinct entity, associated human leukocyte antigen (HLA) Class 2 alleles (HLA-DR4 and -DR1) are distinct from those associated with SLE, SSc, and PM/DM. The most common clinical presentation – Raynaud’s syndrome, arthralgias, swollen hands, sausage-like fingers, and muscle weakness – appear in 90% of patients. More serious organ involvement can lead to pulmonary arterial hypertension, glomerulonephritis, gastrointestinal bleeding, and severe central nervous system involvement. Common treatments include corticosteroids and cyclophosphamide.

Evidence for rituximab to treat MCTD comprises a small case series and case reports. The case series was a retrospective cohort study of 65 pediatric patients who had various autoimmune disorders. Mean age at disease onset was 11 years; mean disease duration before rituximab treatment was three years. Patients were treated with rituximab and followed for at least six
months. Five patients were considered to have a mixed connective tissue disorder – two unclassified, one Sjogren syndrome, and two MCTD. One death three months after starting rituximab in a patient with a mixed connective tissue disorder was attributed to disease progression. Of the four remaining patients with a mixed connective tissue disorder, three attained partial remission, and one had disease progression. Adverse infusion-related events were reported in 12 (18%) of 65 patients, but were not reported separately by disease type. Other evidence comprises case reports.

**Section Summary**

One case series of five patients with mixed connective tissue disorders, three of whom achieved partial remission with rituximab, is insufficient to determine the efficacy and safety of rituximab for the treatment of mixed connective tissue disease (MCTD).

**Multicentric Castleman Disease**

Castleman disease is a rare lymphoproliferative disorder associated with human herpes virus-8 (HHV-8) infection. Prevalence is increased among HIV-infected patients and associated with Kaposi sarcoma, progression to lymphoma, and high mortality in these patients. Castleman disease has two distinct forms with characteristic findings on histological examination: unicentric or localized (hyaline vascular histology), and multicentric (plasma cell infiltrate). Clinical presentation typically involves lymphadenopathy and multi-organ involvement with an aggressive course. In HIV-noninfected patients, multicentric Castleman disease typically presents after age 70 years. For HIV-infected patients, current guidelines suggest IV ganciclovir or oral valganciclovir for treatment of multicentric Castleman disease based on level C evidence. Rituximab is considered an alternative therapy. Other treatments include combination chemotherapy and tocilizumab, a monoclonal anti-interleukin-6 antibody.

In 2012, Reid et al reviewed the literature on rituximab in patients with HIV-related lymphoma and multicentric Castleman disease. The authors identified one prospective and two retrospective cohort studies of patients with multicentric Castleman disease who were treated with rituximab (total N=69). In the prospective study (N=21), median follow-up was 12 months (range, 1-49), and estimated two-year overall survival (OS) was 95%. Of 11 patients who had Kaposi sarcoma at baseline, progression occurred in four (36%). No Grade 3 or 4 adverse events were reported. One retrospective study compared the incidence of subsequent non-Hodgkin lymphoma (NHL) in 33 rituximab-treated patients with the incidence in non-rituximab-treated patients. All rituximab-treated patients had received first-line chemotherapy (etoposide, vinblastine, and anthracyclines). Three-year NHL incidence was 0.04% in the rituximab group compared with 23% in non-rituximab-treated patients. Median OS was 15.7 years and 5.2 years in the rituximab and control groups, respectively. Kaposi sarcoma recurred in four (27%) of 11 patients. Mild to moderate infections occurred in 27% of rituximab-treated patients. A second retrospective study reported sustained complete remission for more than one year in 13 (87%) of 15 rituximab-treated patients compared with less than 50% in non-rituximab-treated patients.

Gerard et al (2012) reported on a prospective cohort of 113 HIV-infected patients who had multicentric Castleman disease. The authors compared the incidence of subsequent NHL in rituximab-treated (n=48) with that in non-rituximab-treated (n=65) patients. At mean follow-up of 4.2 years, annual NHL incidence was 0.004% (4.2 per 1000 person-years) in the rituximab
group and 7% (69.6 per 1000 person years) in the control group (hazard ratio [HR], 0.09 [95% CI, 0.01 to 0.70]). Two- and five-year OS was 93% (95% CI, 80 to 98) and 90% (95% CI, 76 to 96), respectively, in the rituximab group, and 68% (95% CI, 54 to 79) and 47% (95% CI, 32 to 61), respectively, in the control group. Ten Kaposi sarcoma exacerbations and one newly diagnosed Kaposi sarcoma were observed in nine patients after rituximab therapy. Among 36 rituximab responders, multicentric Castleman disease recurred in eight (22%) after a median of 10.5 months.

In 2011, Hoffman et al published a retrospective review of 23 rituximab-treated and 29 non-rituximab-treated HIV-infected patients who had multicentric Castleman disease. At mean follow-up of 2.3 years, mean estimated OS was not reached in the rituximab group and was 5.1 years in the control group (p=0.03). An earlier systematic review of the literature identified 25 case series and case reports of HIV-infected patients who had multicentric Castleman disease (total N=84, 20 [24%] pre-HAART and 64 [76%] post-HAART). Seven (9%) of 75 patients for whom data on treatment were available received rituximab as first-line (n=2) or second-line (n=5) therapy. Complete response occurred in five patients (81%).

One case report of rituximab in multicentric Castleman disease in an HIV-uninfected patient was identified. Complete remission was achieved after four cycles of rituximab and followed by four months of corticosteroid maintenance therapy. Recurrence was not detected during more than four years of follow-up.

Section Summary
Evidence for rituximab in multicentric Castleman disease comes almost exclusively from the HIV literature, which reflects the epidemiology of the disease. Prospective and retrospective cohort studies reported reduced incidence of subsequent non-Hodgkin lymphoma and substantially improved overall survival (>93% at two years in two studies; 90% at five years in one 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 (MS)
A 2013 Cochrane review by He et al identified one RCT of rituximab in relapsing-remitting MS (RRMS). The Phase 2, double-blind, placebo-controlled HERMES trial (2008) enrolled 104 adults (age 18-55 years) with RRMS, at least one relapse during the preceding year, and an Expanded Disability Status Scale (EDSS) score of 0-5.0 (median, 2.5 indicating mild disability) at trial entry. Patients were randomized 2:1 to receive two doses of rituximab 1000 mg IV two weeks apart or placebo. The primary efficacy end point was the total number of gadolinium-enhancing lesions on serial T1-weighted MRI brain scans (markers of acute inflammatory changes) at weeks 12, 16, 20, and 24. Planned follow-up was 48 weeks; although 92% of patients completed 24 weeks of follow-up, only 76% completed 48 weeks. Withdrawals were greater in
the placebo group (40% vs 16% in the rituximab group). Patients who withdrew without having a relapse were considered to be relapse-free. The primary end point was a statistically significantly reduced in the rituximab group (stratified van Elteren test, p<0.001) as was the number of new gadolinium-enhancing lesions over the same interval (stratified van Elteren test, p<0.001). Fewer patients in the rituximab group than in the placebo group relapsed within 24 weeks (34% vs 15% placebo; stratified chi-square test, p=0.02) and 48 weeks (20% vs 40% placebo; stratified chi-square test, p=0.04). Annualized relapse rates were statistically different at week 24 (0.4 [90% CI, 0.2 to 0.6] rituximab vs 0.8 [90% CI, 0.5 to 1.3] placebo) but not at week 48 (0.4 [90% CI, 0.2 to 0.6] rituximab vs 0.7 [90% CI, 0.5 to 1.1] placebo). Disability progression was not assessed.

More patients in the rituximab group (78%) than in the placebo group (40%) had adverse events within 24 hours after the first infusion (e.g., chills, headache, nausea, pyrexia). Most (93%) were mild or moderate. The most common infection-associated adverse events (>10% in the rituximab group) were nasopharyngitis (20% vs 17% placebo), upper respiratory tract infections (19% vs 17%), urinary tract infections (15% vs 9%), and sinusitis (13% vs 9%). Limitations of the study included a high and disproportionate number of withdrawals, lack of sensitivity analyses, and short duration of follow-up. Lack of a disability progression outcome (e.g., change in EDSS) is considered a shortcoming in light of recent evidence that MRI changes and relapse rates are poor predictors of long term disability.

Castillo-Trivino et al (2013) reviewed studies of rituximab for relapsing and progressive forms of MS. They identified four studies, including the HERMES RCT described above two small cohort studies in RRMS (total N=56), and one RCT in primary-progressive MS (PPMS). The Phase 2/3, double-blind, placebo-controlled OLYMPUS trial (2009) enrolled 439 adults (age 18-65 years) with PPMS for at least one year and EDSS score of 2.0-6.5 (median, 5.0 indicating moderate to severe disability with impairment of daily activities). Patients with a history of relapse were excluded. Patients were randomized 2:1 to receive two doses of rituximab 1000 mg IV two days apart every six months for four courses (eight doses). The primary endpoint was time to confirmed disease progression, defined as an increase in EDSS of 1.0 point or more (0.5 point or more if baseline EDSS was >5.5 points) sustained for at least 12 weeks. Planned follow-up was 96 weeks for efficacy and 122 weeks for safety. Eighty-three percent of patients completed 96 weeks and 77% completed 122 weeks of follow-up. Time to disease progression did not differ statistically between rituximab and placebo groups (HR, 0.77 [95% CI, 0.55 to 1.09]; stratified log-rank test, p=0.144). At 96 weeks, increase in T2 lesion volume on MRI brain scan (a marker of past disease activity) was less in the rituximab group than in the placebo group (adjusted Friedman ranked analysis of variance, p<0.001). The incidence of Grade 3 or higher adverse events was 40% in the rituximab group and 38% in the placebo group. Serious infections occurred in 5% and <1% of the rituximab and placebo groups, respectively. Incidences of infusion-associated adverse events within 24 hours of the first dose were 67% and 23% in the rituximab and placebo groups, respectively. Most were mild to moderate.

Section Summary
One RCT in patients with RRMS showed improvements in MRI and clinical outcomes at 24 weeks of follow-up. However, methodological limitations restrict the conclusions that can be
based on this data. One well-designed RCT in patients with PPMS demonstrated no effect of rituximab on disease progression.

**Neuromyelitis Optica**

Neuromyelitis optica (NMO) is a rare autoimmune inflammatory disorder that selectively affects the spinal cord and optic nerves; clinical presentation, characterized by severe optic neuritis that can lead to blindness and transverse myelitis that can lead to paralysis, therefore overlaps with MS. However, clinical course typically is more severe than in MS, and often fatal, and treatments may differ. An autoantibody to aquaporin 4, a water channel found in high concentrations at the blood-brain barrier, is included in NMO diagnostic criteria. Curative treatment does not currently exist; treatment goals are relapse remission, relapse prevention, and symptom relief. Immunosuppression with azathioprine or mycophenolate mofetil (MMF) is commonly used for relapse prevention. Rituximab is being studied for relapse prevention in NMO.

In 2012, Sato et al published an evidence-based review of NMO treatments. Literature was searched through June 2011, and 10 case reports, case series, and retrospective reviews of rituximab treatment were identified. Studies generally showed reductions in annualized relapse rates (from 1.7-5.0 at baseline to 0-0.6 post-treatment) and improvements in EDSS, except in severely disabled patients (e.g., baseline EDSS=8.7) for whom neurological damage may be irreversible. Dosing regimen was commonly 375 mg/m² followed by 1000 mg biweekly for two weeks either as scheduled semi-annual maintenance doses or as-needed. Two of the largest series (total N=55 patients) had follow-up of 19 and 24 months. In one study, disability stabilized or improved in 80% of patients, and in the other, 70% of patients were relapse-free for 24 months. Of 55 patients, one death due to septicemia occurred (1.8%). No cases of posterior reversible encephalopathy syndrome were observed.

In a retrospective review of 90 patients with NMO and NMO spectrum disorders (seropositive for anti-aquaporin-4 IgG but lack other criteria for diagnosis) treated at the Mayo Clinic and Johns Hopkins Hospital, Mealy et al (2014) reported reductions in annualized relapse rate of 88% with rituximab, 87% with MMF, and 72% with azathioprine. Failure rates were 33% with rituximab, 36% with MMF, and 53% with azathioprine. Most patients were previously-treated, e.g., with prednisone, beta-interferon, glatiramer acetate, and IVIG.

**Section Summary**

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

Pemphigoid diseases include eight blistering disorders characterized by auto-antibodies directed against the epidermal basement membrane: bullous pemphigoid, mucous membrane pemphigoid, pemphigoid gestationis, linear IgA disease, epidermolysis bullosa acquisita, anti-laminin g1/anti-p200 pemphigoid, lichen planus pemphigoides, and pemphigoid with renal insufficiency. Pemphigus, in contrast, comprises three major forms characterized by auto-antibodies directed against epidermal cell junctions: pemphigus vulgaris, pemphigus foliaceus, and paraneoplastic pemphigus. Both classes of disease are characterized by blisters and erosions. However, pemphigoid blisters are subepidermal and therefore tense, and pemphigus blisters are more superficial and therefore flaccid or often ruptured. Nikolsky sign – exfoliation and blister formation with skin friction – is negative in pemphigoid diseases and positive in pemphigus.

In 2009, Peterson and Chang published a literature review of rituximab for autoantibody-mediated blistering skin diseases. Literature was searched through August 2007, and 71 patients in case series and case reports were identified. Patients had both pemphigoid diseases (four epidermolysis bullosa acquisita and one bullous pemphigoid) and pemphigus diseases (52 pemphigus vulgaris, including one pemphigus vegetans, a localized form of pemphigus vulgaris, nine pemphigus foliaceus, and five paraneoplastic pemphigus). Fifteen (21%) of 71 patients received rituximab monotherapy; 56 (79%) received concomitant systemic corticosteroids, immunosuppressive drugs, and/or IV immunoglobulin (IVIG). Overall, 49 patients (69%) had a CR, 18 (25%) had a PR, and four (6%) had progressive disease (two patients with paraneoplastic pemphigus, one with pemphigus foliaceus, and one with pemphigus vegetans). Of six deaths associated with rituximab, four occurred in patients with paraneoplastic pemphigus, which typically is resistant to conventional treatment if the primary tumor is not eradicated. One death occurred in a patient with pemphigus vulgaris who developed pneumonia, and one death occurred in a patient with bullous pemphigoid and graft-versus-host disease who developed sepsis. Infections (pneumonia and infective arthritis) also were reported in two other patients with pemphigus vulgaris who received rituximab in combination with corticosteroids and immunosuppressive drugs. Overall incidence of infections was 7%. Noninfectious adverse events were atrial fibrillation, congestive heart failure, and deep venous thrombosis. Of 52 patients with pemphigus vulgaris, 25 (48%) received rituximab monotherapy or combination therapy with IVIG; all 25 patients responded to treatment with no adverse events reported.

**Pemphigoid**

Schmidt et al (2013) reviewed the clinical presentation, diagnostic work-up, and treatment options for pemphigoid diseases. The authors found evidence for rituximab in refractory bullous pemphigoid in combination with first line treatments, such as topical or oral corticosteroid and some immunosuppressive drugs (Level C evidence, based on small case series, case reports, and expert opinion); refractory mucous membrane pemphigoid in combination with immunosuppressive drugs, such as dapsone and/or sulfasalazine (Level B evidence, based on poor-quality controlled trials and large case series); and refractory epidermolysis bullosa acquisita in combination with systemic corticosteroids (Level C evidence).

Shetty and Ahmed (2013) reviewed the literature on rituximab for treatment of refractory bullous pemphigoid. Sixteen patients (one case series and eight case reports), including four children,
(mean age, 6.4 years; range, 5 months-14 years) were identified. Fourteen patients (88%) received rituximab 375 mg/m² weekly for four doses, and two patients (12%) received 1000 mg IV every other week for two doses. All patients received concomitant immunosuppressive therapy and/or IVIG. Mean follow-up was 15.6 months (range, 1-36). Eleven (69%) of 16 patients had a CR, one (6%) had a PR, one (6%) had no response, and three (19%) died. Deaths were due to sepsis in two patients (one child) and cardiac adverse effects. Three patients (19%) had serious infections.

Shetty and Ahmed (2013) also reviewed the literature on rituximab for treatment of refractory mucous membrane pemphigoid. Studies that dosed rituximab at 375 mg/m² weekly for four weeks were included. Twenty-eight patients (one case series and six case reports) were identified. Median follow-up ranged from nine to 31 months. All patients received concomitant immunosuppressive and/or immunoabsorbent therapy. Twenty (71%) of 28 patients had a CR, three (11%) had a PR, two (7%) were nonresponders, and one patient (4%) who had progression of disease leading to blindness was considered a treatment failure. One patient died from infection (pyelonephritis and tuberculosis). Approximately half of patients received a second rituximab cycle because of relapse or lack of response.

Foster et al (2010) reported a retrospective comparative study of 12 patients who had refractory mucous membrane pemphigoid of the eye (ocular cicatricial pemphigoid), 10 of whom were blind in one eye. Six patients received rituximab 375 mg/m² weekly for eight weeks plus IVIG, and six patients received immunosuppressive therapy (cyclophosphamide or infliximab) plus IVIG. At median follow-up of approximately 11 months, visual acuity was preserved and no progression of disease was observed in the rituximab group. In contrast, all six control patients had progressed to blindness in both eyes. No adverse events were observed in the rituximab group.

**Pemphigus**

Cianchini et al (2012) reported on 42 patients who had refractory pemphigus vulgaris with severe mucous or mucocutaneous involvement (n=37) or pemphigus foliaceus (n=5). Patients received rituximab 1000 mg/m² every two weeks for two doses plus corticosteroids only; IVIG or immunosuppressive drugs were not given. At median follow-up of 26.5 months (range, 12-51), 36 (86%) of 42 patients achieved a CR and discontinued steroids within six months. Six patients (14%) had a PR and achieved CR after an additional infusion of rituximab 500 mg IV. Twenty patients (48%) relapsed (time to relapse, eight to 64 months), each of whom received an additional infusion of rituximab 500 mg IV and achieved a CR. No serious adverse events were observed.

**Section Summary**

Evidence for rituximab in pemphigoid and pemphigus diseases comprises case reports, case series, and one 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%-19% of patients, but adverse event reporting may have been incomplete. Only three of eight 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 (e.g., blindness) or death, reported response rates were high, and treatment options in refractory patients are limited. For these reasons, rituximab may be considered medically necessary for treatment of the pemphigoid and pemphigus diseases reviewed in the literature in treatment-refractory patients.

**Primary Sjogren Syndrome**

Sjogren syndrome is an autoimmune disorder characterized by lymphocytic infiltration and progressive destruction of the exocrine glands of the body, specifically the salivary and lacrimal glands, which cause xerostomia (dry mouth) and keratoconjunctivitis sicca (dry eyes). Extraglandular disease leads to vaginal dryness, chronic bronchitis, and dry skin, and may affect the kidneys, blood vessels, liver, pancreas, peripheral nervous system (distal axonal sensorimotor neuropathy), and central nervous system. Sjogren syndrome often accompanies other autoimmune disorders, such as rheumatoid arthritis and lupus. The condition is most common in women older than 40 years. Treatment focuses on symptom relief; corticosteroids, immunosuppressive drugs, or IVIG may be prescribed for severe complications.

In 2010, Ramos-Casals et al published a systematic review of treatments for primary Sjogren syndrome. Literature was searched through April 2010, and two small (total N=47) RCTs plus several uncontrolled studies were identified. The RCTs compared rituximab to placebo for symptoms of xerostomia and fatigue. Statistically significant improvements in primary end points were not achieved with rituximab 1000 mg biweekly for two doses, although other symptoms, e.g., dry eye, showed significant improvements. Uncontrolled studies have shown improvements in extraglandular features, such as vasculitis, neuropathy, and glomerulonephritis.

A 2014 blinded RCT by Devauchelle-Pensec et al randomized 120 patients with primary Sjogren syndrome and at least one extraglandular manifestation to rituximab 1000 mg weekly for two doses or placebo, and assessed response in global disease, pain, fatigue, and dryness at 24 weeks. Mean (SD) baseline European Sjogren Syndrome Disease Activity Index (ESSDAI, a validated 0 [no symptoms] to 49 [high disease activity] scale of systemic disease activity in patients with Sjogren syndrome) score was 10. Baseline corticosteroids (30% of patients) and methotrexate (20% of patients) were discontinued four weeks before trial entry. By pre-specified response criteria (≥30 mm improvement in two of four symptom VASs at week 24), a statistically significant between-group difference was not observed. A statistically significant difference in proportion of responders was observed at six weeks and in reduction of fatigue at six and 16 weeks, both favoring rituximab. Serious infection occurred in 3% of rituximab-treated patients and 9% of controls, but overall serious adverse events occurred more commonly in rituximab-treated patients (21% vs 14% control). Infusion reactions occurred in 8% of rituximab-treated patients and 2% of controls.

In a 2013 nonrandomized study, Carubbi et al compared rituximab (six courses at six-month intervals of rituximab 1000 mg biweekly for two doses; n=19) with conventional disease-modifying anti-rheumatic drugs (DMARDs [hydroxychloroquine, methotrexate, or cyclosporine]; n=22) in patients with early-onset primary Sjogren syndrome. A minimum ESSDAI score of six was required for study entry (median, 20 [range, 6-41]). Median disease duration was 14 months (range, 6-21). DMARDs and corticosteroids were discontinued at least six months before baseline, except for patients with severe extraglandular manifestations needing...
continuation of treatment, with no change in dosage allowed. At 24 weeks, mean reduction from baseline ESSDAI was significantly greater with rituximab than with DMARD therapy, and this difference was maintained through 120 weeks of follow-up.

In 2012, Mekinian et al published two registry studies of patients with primary Sjogren syndrome and involvement of the central or peripheral nervous system. Patients were drawn from the French Autoimmunity and Rituximab (AIR) registry, a prospective cohort study of rituximab in autoimmune diseases. Of 11 patients with central nervous system involvement (e.g., MS-like symptoms [n=6], cognitive dysfunction [n=3]), only one patient with cyclophosphamide-refractory transverse myelitis reported improvement in ability to walk, and one patient with anxiety and depression reported subjective improvement. Of 17 patients with peripheral nervous system involvement (sensorimotor neuropathy [n=11], sensory neuropathy [n=4], and multineuritis [n=2]), physician-assessed neurological improvements occurred in 11 patients (65%) at three months and persisted in nine patients (53%) at six months. Statistically significant improvements in objective measures (Rankin scale, a 0 [no symptoms] to six [dead] scale of overall neurological function, and ESSDAI) were observed at three, six, and nine months. Physician-assessed improvements at three months and change in ESSDAI at six months were statistically greater in patients with cryoglobulinemia and/or vasculitis.

In 2013, Gottenberg et al published an updated report of the AIR registry. Of 78 enrolled patients, 74 (95%) had systemic involvement of disease. At median follow-up of 35 months, statistically significant reductions in corticosteroid usage and ESSDAI were observed, and physician-assessed improvements after one cycle of rituximab were reported in 60% of patients. In contrast with the earlier studies by Mekinian et al, improvements in both central and peripheral neuropathy were observed. Half of patients required rituximab re-treatment. Infusion reactions and delayed serum sickness-like disease leading to discontinuation of rituximab occurred in five patients (6%). Three serious infections (1.3 per 100 patient-years) and two cancer-related deaths occurred.

Section Summary

Patients with primary Sjogren syndrome who require more than symptomatic treatment for severe glandular or extraglandular disease are generally treated with corticosteroids and immunosuppressive drugs. Rituximab has been studied in a small number of patients in randomized and nonrandomized trials and observational studies. Efficacy of rituximab was not consistently demonstrated, e.g., a large (N=120) randomized trial showed no difference in response compared with placebo in mostly untreated patients, and a small (N=41) nonrandomized trial showed statistically significant differences in response compared with disease-modifying anti-rheumatic drugs in previously-treated patients. Incidence of adverse events did not appear to be increased above that observed in other patient populations. Given the limited treatment options and potential serious outcomes, including death, for patients with refractory disease, rituximab may be considered medically necessary for these patients. Well-designed randomized trials comparing rituximab with alternative treatments for first-line and second-line therapy of primary Sjogren syndrome are needed.
Systemic Lupus Erythematosus (SLE)

One RCT, EXPLORER, and several systematic reviews were identified. A 2014 systematic review examined several biologic agents and included only two rituximab studies, the EXPLORER and LUNAR trials, which are described below. Three systematic reviews that included the full publication of the EXPLORER trial are summarized in Table 2. These comprised mostly prospective and retrospective cohort studies and case series. Most patients had refractory SLE. Rituximab dosing regimens and definitions of response, flare, and relapse varied across studies. Duxbury et al observed that this heterogeneity contributed to the “discrepancy in the perceived efficacy of rituximab between controlled [studies, which generally reported lower response rates] and observational studies [which generally reported higher response rates].”

Table 2: Systematic Reviews of Rituximab in Systemic Lupus Erythematosus

<table>
<thead>
<tr>
<th>Study</th>
<th>N/n</th>
<th>Follow-Up, months</th>
<th>Efficacy</th>
<th>Adverse Eventsa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cobo-Ibanez 2014</td>
<td>25°(1 RCT)/1231</td>
<td>range, 2-103</td>
<td>CR/PR: 64%-91%</td>
<td>TTR: 4-18 m, Serious infections: 7%-13%</td>
</tr>
<tr>
<td>Duxbury 2013</td>
<td>30 (3 RCTs)/1243</td>
<td>range, 2-38</td>
<td>PR: 31%-38%</td>
<td>SAEs: 11.5%</td>
</tr>
<tr>
<td>Lan 2012</td>
<td>21 (2 RCTs)/1012</td>
<td>median, 18.2</td>
<td>PR: 25%</td>
<td>CR: 33%</td>
</tr>
</tbody>
</table>

CR: complete response; n, months; N/n: number of studies/number of patients; PR: partial response; SAE: serious adverse event; TTR: median time to relapse

a In rituximab-treated patients.
b A post-hoc analysis of the RCT is not counted as a separate study here.
c Included EXPLORER, LUNAR, and a Spanish-language RCT that found no difference between rituximab and cyclophosphamide in 19 patients with severe SLE.

The 2010 EXPLORER (Exploratory Phase 2/3 SLE Evaluation of Rituximab) double-blind RCT enrolled patients with moderate to severe extra-renal lupus despite background immunosuppressive therapy. Patients (N=257) were randomized 2:1 to rituximab 1000 mg IV at weeks 1, 3, 24, and 26 or placebo in combination with prednisolone and either azathioprine, MMF, or methotrexate. At one year of follow-up, there was no statistical between-group difference in clinical response as defined by improvement in (British Isles Lupus Assessment (BILAG) score; BILAG measures overall and organ-specific disease activity on a scale from A (severe) to E (unaffected). Seventy percent of the rituximab group and 72% of the placebo group had no clinical response; major clinical response (improvement from BILAG A to BILAG C in all organs at 24 weeks and maintenance of this response without moderate or severe flare to week 52) were achieved by 12% and 16% of the rituximab and placebo groups, respectively. In prespecified subgroup analysis, African-American or Hispanic patients (n=96) who received rituximab achieved more major and partial responses (14% and 20%, respectively) compared with those in the placebo group (9% and 6%, respectively; stratified Wilcoxon rank sum test, p=0.041). However, because there was no correction for multiple comparisons, this result requires duplication. Safety and tolerability were similar in both groups. In 2011, the authors reported a post hoc analysis using alternative definitions for flare in the 72% of patients (N=185) who achieved low disease activity (BILAG C or better) at any point before week 52. When mild (BILAG A) flares alone were examined, rituximab reduced the risk of a first subsequent A flare and reduced mean annualized A flare rates.
Lupus Nephritis (LN)

LN is among the most serious complications of SLE. It occurs in approximately half of SLE patients and is associated with a poor prognosis. Estimated five-year survival among patients with International Society of Nephrology/Renal Pathology Society (ISN/RPS) class IV (diffuse) LN is 80% and among all SLE patients, 86% (86); 5%-10% of LN patients will progress to end-stage renal disease at 10 years. Current treatment regimens include cyclophosphamide or MMF, both administered with corticosteroids. Response rates at 1 year are approximately 50%-80%, but these are often only partial.

Evidence for the use of rituximab in LN comprised two systematic reviews, one RCT, one registry study, and several case series and case reports.

A 2013 systematic review with meta-analysis included 26 RCTs of induction and maintenance treatments for proliferative LN. Two RCTs (total N=163) that compared the addition of rituximab to either MMF or cyclophosphamide versus MMF or rituximab alone, respectively, were identified. Neither study showed a difference in response rates or incidence of any adverse events at one year.

Randomized trial data for the use of rituximab in refractory LN were not identified. A 2013 systematic review of rituximab in refractory LN included nine prospective comparative studies, nine retrospective studies, and eight case series and case reports (total N=300). Thirty-nine percent of patients had class IV nephritis, but 30% were unclassified. Rituximab dosing and use as alternative or add-on therapy (to cyclophosphamide, MMF, azathioprine, or methotrexate) varied across studies; the most common dosing regimen was 375 mg/m² weekly for four weeks. Mean follow-up was 60 weeks (range, 12-120). Rituximab induced a complete, partial or no response (using American College of Rheumatology and European League Against Rheumatism standard definitions in most studies) in 40%, 34% and 26% of cases, respectively. Complete responses and any responses (complete or partial) were most frequent in patients with class III (focal) LN and least frequent in patients with class V (membranous) LN.

One of the RCTs identified in the meta-analysis described above was the 2012 double-blind LUNAR trial (Lupus Nephritis Assessment with Rituximab). LUNAR was a randomized, double-blind, placebo-controlled Phase 3 trial of rituximab added to MMF plus corticosteroids as initial therapy for proliferative LN. The trial included 144 patients 16 to 75 years of age who had histologic evidence of class III or IV LN on biopsy within 12 months before randomization. Patients were randomized to receive rituximab 1000 mg IV at weeks 1, 3, 24, and 26 or placebo in combination with MMF and prednisone. The primary efficacy end point, superior (complete or partial) renal response rate at one year with rituximab, was not reached. Overall (complete and partial) renal response rates were 57% and 46% in the rituximab and placebo groups, respectively (chi-square test, p=0.18). Incidence of serious adverse events did not differ statistically between groups.

In 2012, Diaz-Lagares et al reported pooled results from the UK-BIOGEAS Registry and from published European studies. The UK-BIOGEAS Registry was jointly developed by the U.K. and Spain to evaluate the use of rituximab in LN. Among a total of 164 patients (99 Registry patients and 65 patients in published studies), most (57%) had class IV LN. Rituximab was administered
in combination with corticosteroids in 99% of patients and with immunosuppressive agents (cyclophosphamide or MMF) in 76% of patients. Half of patients were refractory to standard treatment, 42% were treated for disease flare, and 8% were treated at first presentation of LN. At six and 12 months, respectively, renal response rates (using standard definitions) were 27% and 30% for CR, 40% and 37% for PR, and 33% at both time points for no response. Overall (complete or partial) responses were more common in patients with class III LN than in patients with class IV or class V LN (chi-square test, p=0.007 and 0.03, respectively). Two patients (1%) developed severe infusion reactions. Twenty patients (12%) had 21 infections: seven respiratory infections (four pneumonia, three respiratory tract infections), five sepsis, two urinary tract infections, two osteoarticular infections (one septic arthritis, one necrotizing fascitis), four viral infections (three herpes zoster, one CMV viremia), and one pneumococcal meningitis. Six patients (4%) developed neutropenia (three [2%] febrile neutropenia) after rituximab administration. Three patients (2%) developed posterior reversible leukoencephalopathy.

Section Summary
Evidence for rituximab in patients with refractory SLE comprises one large RCT that did not show improved response rates at one year with rituximab add-on therapy. Systematic reviews include mostly cohort studies and case series that generally report higher response rates than controlled studies. Rates of serious and severe adverse events, mostly infections and infusion or allergic reactions, were 7%-13%. Given the limited treatment options and potential serious outcomes, rituximab may be considered medically necessary for these patients.

Evidence for rituximab in new or refractory lupus nephritis comprises two RCTs that did not show improved response rates at one year with rituximab combination or monotherapy compared with standard immunosuppressants. Summaries of noncomparative studies reported complete and partial response rates of 30%-40% and approximately 35%, respectively, in patients with mostly refractory disease. Given the limited treatment options and potential serious outcomes, rituximab may be considered medically necessary for these patients.

Systemic Sclerosis (Scleroderma)
Jordan et al (2014) conducted a multicenter case-control study of patients with scleroderma who were enrolled in the European Scleroderma Trial and Research (EUSTAR) database. Sixty-three rituximab-treated patients were matched with non-rituximab-treated controls on scleroderma subtype (diffuse or limited), baseline forced vital capacity (FVC), baseline Modified Rodnan Skin Score (MRSS), disease duration, follow-up duration, and immunosuppressive therapy. Fifty-six percent of patients had severe diffuse scleroderma. The most frequent dose of rituximab was 1000 mg IV weekly for two weeks. Immunosuppressive therapies included prednisone, methotrexate, azathioprine, MMF, and cyclophosphamide. Median follow-up was seven months (IQR, 4-9). Mean (SD) improvement in MRSS was 24.0 (5.2) percentage points in 25 rituximab-treated patients and 7.7 (4.3) percentage points in matched controls (paired t-test, p=0.03). Treatment effect exceeded an anchor-based minimally important difference of 5.3 percentage points reported by Khanna et al. Mean (SD) FVC increased 0.4 (4.4) percentage points in nine rituximab-treated patients and decreased 7.7 (3.6) percentage points in matched controls (paired t-test, p=0.02). Mean (SD) improvement in diffusing capacity of carbon monoxide (DLCO) did not differ statistically between groups (3.7 [1.4] percentage points in the rituximab group and 6.2
[6.2] percentage points in the control group; paired t-test, p=0.9). Infections occurred in 21% of rituximab-treated patients, and serum sickness/hypersensitivity reaction in 4%.

In 2011, Phumethum et al reviewed the literature on biologic therapies to improve inflammatory arthritis, disability (as assessed by the Health Assessment Questionnaire Disability Index [HAQ-DI]), and skin symptoms in patients with systemic sclerosis. Literature was searched in early 2010, and six studies of rituximab (one controlled trial [reviewed below], three cohort studies, and three case reports; total N=36) were identified. No study reported improvements in HAQ-DI, and resolution of joint pain was reported in one patients. Improvements in skin score were observed in some rituximab-treated patients, but effect size was smaller than in the control arm of the RCT. Incidences of infusion reactions and respiratory tract infections were 47% and 29%, respectively, in one study each.

Daoussis et al (2010) assigned (by birth date) 14 patients with diffuse scleroderma to standard treatment plus two cycles of rituximab (375 mg/m² weekly for four doses) six months apart (n=8) or standard treatment alone (n=6). Assignments were unblinded. Standard treatments included prednisone, bosentan, MMF, and cyclophosphamide. Statistically significant improvements in pulmonary function tests, but not in skin symptoms, were observed with rituximab compared with control. At one year of follow-up, median FVC increased 10.3 percentage points (IQR, 6.2-18.7) in the rituximab group and decreased 5.0 percentage points (IQR, 4.1-11.6; Wilcoxon matched pairs test, p=0.002) in the control group. Median DLCO increased 19.5 percentage points (IQR, 3.7-30.8) in the rituximab group and decreased 7.5 percentage points (IQR, 1.4-26.6) in the control group (Wilcoxon matched pairs test, p=0.023). Median improvement in Modified Rodnan Skin Score was 39.3 percentage points (IQR, 27.3–65.0) in the rituximab group and 20.8 percentage points (IQR, 10.8–39.3) in the control group (Wilcoxon matched pairs test, p=0.06).

Section Summary
Evidence for rituximab in systemic sclerosis comprises observational studies and one small, unblinded trial. Improvements were seen in skin symptoms and pulmonary function tests with rituximab, but results require replication in larger, blinded trials to rigorously assess effective dosing of rituximab in scleroderma and adverse effects.

Transplantation
Graft-Versus-Host Disease (GVHD)
Rituximab has been studied primarily for steroid-refractory chronic GVHD. Chronic GVHD, historically defined as occurring more than 100 days after transplant, is the primary cause of late morbidity and mortality after allogeneic hematopoietic stem cell transplantation (allo-SCT). Approximately half of patients respond to first-line treatment (systemic corticosteroid with or without a calcineurin inhibitor), but treatment options for steroid-refractory disease are limited, and prognosis is poor.

In 2009, Kharfan-Dabaja published a systematic review and meta-analysis of seven cohort studies (total N=111) of rituximab in chronic GVHD. Three studies were prospective and four were retrospective. Pooled overall response rate was 66% (95% CI, 57 to 74). Indication-specific
response rates were 13%-100% for skin, 0-83% for oral mucosa, 0-66% for liver, and 0-38% for lung. Common adverse events were infusion reactions or infectious complications.

In 2010, Kim et al published a multi-center, Phase 2 cohort study of 37 patients with steroid-refractory chronic GVHD diagnosed according to National Institute of Health (NIH) criteria. Most transplants used myeloablative conditioning regimens (78%) and unrelated donor cells. Patients received rituximab 375 mg/m² weekly for four weeks and then monthly for four months; 29 patients completed treatment (four dropped out and four died), and 22 completed eight additional months of follow-up (two dropped out and five died). Thirty-two patients (86%) had any response (complete or partial) at any time during the study; median time to response was 29 days (range, 0-252). Twenty-one patients (57%) maintained response for one year, of whom six discontinued and 15 reduced steroid therapy. Response rate was higher for skin, oral mucosa, and musculoskeletal symptoms (response rate, 71%-100%) than for other organs (e.g., 9% for lung involvement). Most treatment failures were due to infectious complications or relapse of the primary disease.

Two studies examined prophylactic rituximab for the prevention of chronic GVHD after allo-SCT. Cutler et al (2013) administered rituximab 375 mg/m² at 100 days and 3, 6, 9, and 12 months after nonmyeloablative or myeloablative transplantation of HLA-matched related (48%) or unrelated (58%) donor cells (N=65). Most common diagnoses were acute myeloid leukemia (AML) and myelodysplastic syndromes. Systemic immunosuppressants were tapered per institutional standards. Thirty-two patients (49%) received all four rituximab infusions (median, 3); most common reasons for not completing the treatment course were development of GVHD and relapse. All patients had at least two years of follow-up (median, 2 years). Cumulative incidence of chronic GVHD and of steroid-requiring chronic GVHD were 48% and 31%, respectively; in a contemporaneous control cohort of 68 patients who declined participation in the study, corresponding incidences were 60% (log-rank test, p=0.1 vs treatment cohort) and 49% (log-rank test, p=0.015), respectively. Estimated four-year relapse (34%) and non-relapse mortality (5%) may be unreliable due to low patient numbers at follow-up, which were not reported. Two-year cumulative incidence of Grade 3 or higher infections was 15%; one of two lethal infections was considered possibly related to rituximab.

Arai et al (2012) administered rituximab 375 mg/m² on post-transplantation days 56, 63, 70, and 77 to 35 patients who had high-risk chronic lymphocytic leukemia (CLL; n=22) or mantle cell lymphoma (MCL; n=13). Patients received reduced-intensity conditioning with total lymphoid irradiation and anti-thymocyte globulin. Transplants were from matched related (n=19) or unrelated (n=16) donors. Systemic immunosuppressants were tapered and discontinued during the course of rituximab treatment. Median follow-up for patients seen at the study center was four years; median follow-up for study patients was not reported. Incidence of acute GVHD was 6%, cumulative incidence of chronic GVHD was 20%, and nonrelapse mortality was 3%. Four-year OS was 73% for patients with CLL and 69% for patients with MCL. Rituximab-related neutropenia (<500/mcL) developed in 40% of patients, with febrile neutropenia and infection in one patient. Fifteen patients (43%) had severe Grade 3 infections within one year of transplant; none were fatal.
Section Summary
Rituximab for treatment of steroid-refractory chronic GVHD has been examined in cohort studies, which show response in most patients, with sustained response and steroid reduction or discontinuation in some. Treatment options for patients with steroid-refractory GVHD are limited, rituximab may be considered medically necessary in this setting.

Evidence for rituximab prophylaxis for GVHD comprises two small cohort studies, one of which included a contemporaneous control group. Although results suggested that rituximab may reduce the incidence of GVHD, replication in larger, controlled trials is needed. Due to the risk of severe adverse events with rituximab, improved health outcomes in the prophylactic setting cannot be assumed.

Solid Organ Transplantation

Pre-Transplant Desensitization
Patients who are human leukocyte antigen (HLA)-sensitized have broadly reactive alloantibodies, e.g., due to previous pregnancy, transfusion of blood or blood products, or transplantation. HLA-sensitized patients are difficult to match for donor organs because of high risks of hyperacute rejection and graft loss with cross-matched organs (i.e., positive for reactive antigens). Panel reactive antibody (PRA) assays define the level of HLA-sensitization and are used to optimize identification of compatible donors. Some transplant centers employ desensitization protocols to overcome HLA sensitization. Protocols commonly use low-dose IVIG with plasma exchange (IVIG/Plex) or high-dose IVIG.

Vo et al (2014) planned to conduct a double-blind RCT of 90 HLA-sensitized, deceased-donor, renal transplant recipients randomized to pre-transplant desensitization with IVIG plus rituximab or IVIG plus placebo. Of 15 patients enrolled, 13 underwent transplantation. However, after five serious events were observed in seven patients who were randomized to placebo (antibody-mediated rejection [ABMR] in three patients and graft loss in two patients), the trial was halted. No ABMR or graft loss occurred in six rituximab-treated patients. Mean (SD) serum creatinine levels at six and 12 months were 1.7 (0.5) mg/dL and 2.0 (0.6) mg/dL, respectively, in two patients in the placebo group who had surviving allografts, and 1.1 (0.4) at both time points for patients who received rituximab. Although groups were similar at time of transplantation for PRA and donor-specific alloantibody levels, one (17%) of six patients randomized to rituximab had undergone previous transplant compared with five (70%) of seven patients randomized to placebo.

This same group reported three previous cohort studies of induction immunosuppression with rituximab plus IVIG in HLA-sensitized renal transplant recipients (total N= approximately 200). Patient and graft survival was 100% and 94%, respectively, at 12 months; 95% and 84%, respectively, at 24 months; and 95% and 88% (deceased donor transplants) at 48 months. Mean (SD) serum creatinine at 12, 24, and 36 months was 1.5 (1.1) mg/dL, 1.3 (0.3) mg/dL, and 1.3 (not reported) mg/dL, respectively. In comparison, estimated three-year survival of a contemporaneous cohort of 3754 highly sensitized (PRA >80%) patients with end-stage renal disease who were wait-listed for transplants and remained on dialysis was 79%.
Opportunistic infection with polyomavirus BK (BKV) occurs in 10%-20% of kidney transplants and can cause nephropathy, rejection, and graft dysfunction and failure. Barbosa et al (2014) compared two cohorts of kidney transplant recipients (63% deceased donor) for post-transplant emergence of BKV. One cohort (n=187) comprised HLA-sensitized patients who underwent pre-transplant desensitization with IVIG plus rituximab; the other cohort (n=284) comprised non-HLA-sensitized patients. More patients in the desensitized group received lymphocyte-depleting immunosuppression induction (i.e., with anti-thymocyte globulin or alemtuzumab; 78%) than in the non-desensitized group (38%). At two years post-transplant, BKV viremia occurred in 20% of desensitized patients and 10% of non-desensitized patients. Patient survival, graft survival, and incidence of BKV-associated nephropathy did not differ statistically between groups.

**Antibody-Mediated Rejection (Abmr)**

Antibody-mediated injury to allografts comprises ABMR, ABMR without complement deposition, antibody-mediated endarteritis, and accelerated arteriosclerosis of allografts. Induction immunosuppressive regimens initiated before, at the time of, or immediately after transplantation, mute T-cell responses to antigen presentation, reducing acute rejection. Induction regimens typically are combination high-dose immunosuppressive agents or anti-T cell antibodies (e.g., anti-thymocyte globulin) plus lower-dose immunosuppressive agents.

**Induction To Prevent Abmr**

Zhao et al (2014) conducted a systematic review with meta-analysis of rituximab-containing induction regimens in HLA-sensitized kidney transplant recipients. Literature was searched through July 2013, and seven comparative studies (total N=589) were identified. Studies varied by design (retrospective or prospective), sample size (40-144 patients), induction regimens, rituximab dosing, and whether rituximab was add-on or alternative therapy. However, statistical heterogeneity was low. Overall study quality was very low; no prospective, randomized trials were included. In meta-analysis of five studies, acute ABMR occurred less in patients treated with rituximab (n=182) compared with controls (n=212) (odds ratio [OR], 0.52 [95% CI, 0.28 to 0.98]; p=0.04; I²=0%). Meta-analysis of four studies showed increased graft survival at one year in rituximab-treated patients (n=165) compared with controls (n=183) (OR, 3.02 [95% CI, 1.14 to 8.02]; p=0.03; I²=18%).

Tyden et al (2009) conducted a multicenter, double-blind, RCT comparing induction immunosuppressive regimens with and without rituximab in 136 kidney transplant recipients. Patients were randomized to receive a single infusion of rituximab (n=68) or placebo (n=68) within 24 hours before transplantation. All patients also received steroids, tacrolimus, and MMF. At six months after transplant, there was no statistical between-group differences in treatment failures (10 rituximab, 14 placebo; p=0.348), rejection episodes (eight rituximab, 12 placebo; p=0.317), mean (SD) creatinine clearance (67 [3] mL/min rituximab, 66 [3] mL/min placebo), or incidence of infections. At three-year follow-up, eight (12%) of rituximab-treated patients and no placebo-treated patients had died (p=0.006). Deaths were due to fungal pneumonia and lung cancer in one patient each, and six cardiac arrests. Pre-treatment history of cardiovascular disease was similar between groups.
**Treatment Of Abmr**

Roberts et al (2012) conducted a systematic review of acute ABMR treatments in kidney transplant recipients. Two published, low quality studies of rituximab were identified (total N=78). The studies used historical controls and were rated very low quality. Most patients in the two studies received deceased donor allografts. Graft failure occurred in three (8%) of 28 rituximab-treated patients and 14 (35%) of 40 controls.

Ravichandran et al (2013) reported a retrospective case review of 33 cardiac recipients who had clinical suspicion of rejection (signs or symptoms of heart failure and/or hemodynamic compromise), C4d complement staining on endomyocardial biopsy, and absence of grade 2R or greater cellular rejection. Thirteen patients received rituximab and 20 did not. Immunosuppressive regimens varied; all patients received steroids. All rituximab-treated patients (100%) and 80% of controls survived at least one week. At year three, patient survival was 75% and 29% in the rituximab and control groups, respectively (p=0.009). Infections and rehospitalizations occurred in four (31%) and eight (65%) of 13 rituximab-treated patients, respectively, and in two (10%) and seven (35%) of 20 controls.

Zarkhin et al (2008) reported on an open-label RCT of 20 consecutive pediatric patients (age 2-23 years; mean [SD], 14 [6] years) who had biopsy-proven acute rejection with infiltrating B-cell clusters after kidney transplant. Patients were randomized to standard immunosuppressive treatment (pulse steroid and/or anti-thymocyte globulin; n=10) or standard treatment plus rituximab weekly for four doses (n=10). All patients completed rituximab dosing without serious adverse events through 12 months of follow-up. Statistically significant improvements in creatinine clearance were seen in the rituximab group compared with the control group at six and 12 months after treatment (p-value for trend, 0.026).

**Section Summary**

Rituximab has been studied in the setting of solid organ (primarily kidney) transplantation for pre-transplant desensitization, induction immunosuppressive therapy, and treatment of antibody-mediated rejection. Several cohort studies in sensitized individuals demonstrated good patient and graft survival with rituximab desensitization three years after transplant. A randomized, controlled trial (RCT) comparing desensitization regimens with and without rituximab was terminated due to excess serious adverse events in the control arm, and one study reported no increase in polyomavirus BK-associated nephropathy at two years of follow-up. This evidence suggests that health outcomes are improved with rituximab desensitization regimens in sensitized renal transplant candidates.

Evidence for rituximab induction to prevent acute antibody-mediated rejection (ABMR) comprised a meta-analysis of five very low-quality trials and one 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 three years of follow-up. Rituximab has not been shown to improve health outcomes when used for induction immunosuppression in kidney transplant recipients.

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

Summary
Autoimmune Hemolytic Anemia (AIHA)
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 a randomized controlled trial enrolled
patients with previously untreated disease. Response rates were 75%-93%; sustained responses
to three years were observed; relapses occurred in 5%-15% of patients. Serious infections were
observed in 4%-15% of patients. For cold agglutination syndrome (CAS), which generally has a
poorer response than warm AIHA to first-line corticosteroids, a response rate of 62% was
reported. As a potential corticosteroid-sparing agent in warm AIHA and effective treatment for
CAS, rituximab may improve health outcomes. Rituximab is not considered a treatment option
for paroxysmal cold hemoglobinuria.

Idiopathic Thrombocytopenic Purpura (ITP)
Rituximab is being studied as a splenectomy-delaying or -avoiding approach in patients with
ITP. Two systematic reviews of primarily observational studies (one in children [median age, 8
years] and one in adults) and two RCTs in adults investigated mostly non-splenectomized
patients. Overall and complete response rates were approximately 57% and 40%, respectively, in
adults, and 68% and 39% in children. Median response durations were approximately one year.
One RCT of newly-diagnosed patients reported an improved overall response rate with rituximab
in combination with corticosteroid compared with corticosteroid alone, but another did not.
Adverse event reporting was inconsistent; serious infections and hypersensitivity reactions
occurred in 4% of 370 children included in the systematic review. Overall, evidence suggests
potentially improved health outcomes in patients with steroid-refractory ITP who are able to
delay or avoid splenectomy with rituximab treatment.

Thrombotic Thrombocytopenic Purpura (TTP)
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, evidence comprised case series and case reports, summarized in a
systematic review that reported remission in 98% of rituximab-treated patients with a median
follow-up of 10 months. A case series of five patients with recurrent TTP in remission who
received prophylactic rituximab reported maintenance of remission in four patients at nine
months.

This evidence suggests that further study of rituximab in patients with relapsed and refractory
TTP is warranted. However, improved health outcomes have not been shown. Rituximab has rare
but potentially fatal adverse effects. Although TTP also is considered life-threatening,
knowledge about the balance of risks and benefits of rituximab in the acute or prophylactic
setting is currently lacking.
Factor Inhibitors in Hemophilia
Rituximab for factor inhibitor eradication in congenital hemophilia and acquired hemophilia A has been studied in a small number of patients, primarily in case reports and cohort studies. In immune tolerance induction (ITI)-refractory patients with congenital hemophilia and factor inhibitor, complete remission occurred in 53% of patients who received rituximab alone or in combination with continued ITI; a small cohort study supported combination therapy in the refractory setting. A comparative study in acquired hemophilia A did not find improved response rates in patients treated with rituximab alone or in combination compared with standard cyclophosphamide plus cyclosporine. Evidence does not support rituximab as an alternative to standard treatments for factor inhibitor eradication (i.e., 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 adverse events. 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 (HCV)-Associated Cryoglobulinemic Vasculitis
Recent reviews summarized the literature for rituximab to treat hepatitis C virus (HCV)-associated cryoglobulinemic vasculitis. Across two 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 peginterferon-free drug regimens. More effective antiviral treatments should improve outcomes, e.g., virologic and immunologic responses and cure rate of both HCV and associated vasculitis. However, for patients with antiviral-resistant active disease or with severe or life-threatening cryoglobulinemic vasculitis, rituximab in combination with current treatments may improve health outcomes. Viral load and liver function tests should be monitored during rituximab treatment.

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

Multicentric Castleman Disease
Evidence for rituximab in multicentric Castleman disease comes almost exclusively from the HIV literature, which reflects the epidemiology of the disease. Prospective and retrospective cohort studies reported reduced incidence of subsequent non-Hodgkin lymphoma and substantially improved overall survival (>93% at two years in two studies; 90% at five years in one 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 (MS)
One RCT in patients with RRMS showed improvements in MRI and clinical outcomes at 24 weeks of follow-up. However, methodological limitations restrict the conclusions that can be based on this data. One well-designed RCT in patients with PPMS demonstrated no effect of rituximab on disease progression.

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

Pemphigoid and Pemphigus Diseases
Evidence for rituximab in pemphigoid and pemphigus diseases comprises case reports, case series, and one 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%-19% of patients, but adverse event reporting may have been incomplete. Only three of eight 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 (e.g., blindness) or death, reported response rates were high, and treatment options in refractory patients are limited. For these reasons, rituximab may be considered medically necessary for treatment of the pemphigoid and pemphigus diseases reviewed in the literature in treatment-refractory patients.

Primary Sjogren Syndrome
Patients with primary Sjogren syndrome who require more than symptomatic treatment for severe glandular or extraglandular disease are generally treated with corticosteroids and immunosuppressive drugs. Rituximab has been studied in a small number of patients in randomized and nonrandomized trials and observational studies. Efficacy of rituximab was not consistently demonstrated, e.g., a large (N=120) randomized trial showed no difference in response compared with placebo in mostly untreated patients, and a small (N=41) nonrandomized trial showed statistically significant differences in response compared with disease-modifying anti-rheumatic drugs in previously-treated patients. Incidence of adverse events did not appear to be increased above that observed in other patient populations. Given the limited treatment options and potential serious outcomes, including death, for patients with
refractory disease, rituximab may be considered medically necessary for these patients. Well-designed randomized trials comparing rituximab with alternative treatments for first-line and second-line therapy of primary Sjogren syndrome are needed.

**Systemic Lupus Erythematosus (SLE)**
Evidence for rituximab in patients with refractory SLE comprises 1 large RCT that did not show improved response rates at one year with rituximab add-on therapy. Systematic reviews include mostly cohort studies and case series that generally report higher response rates than controlled studies. Rates of serious and severe adverse events, mostly infections and infusion or allergic reactions, were 7%-13%. Given the limited treatment options and potential serious outcomes, for patients with this disease, rituximab may be considered medically necessary for these patients.

**Lupus Nephritis**
Evidence for rituximab in new or refractory lupus nephritis comprises two RCTs that did not show improved response rates at one year with rituximab combination or monotherapy compared with standard immunosuppressants. Summaries of noncomparative studies reported complete and partial response rates of 30%-40% and approximately 35%, respectively, in patients with mostly refractory disease. Given the limited treatment options and potential serious outcomes, for patients with this disease, rituximab may be considered medically necessary for these patients.

**Systemic Sclerosis (Scleroderma)**
Evidence for rituximab in systemic sclerosis comprises observational studies and one small, unblinded trial. Improvements were seen in skin symptoms and pulmonary function tests with rituximab, but results require replication in larger, blinded trials to rigorously assess effective dosing of rituximab in scleroderma and adverse effects.

**Graft-Versus-Host Disease (GVHD)**
Rituximab for treatment of steroid-refractory chronic GVHD has been examined in cohort studies, which show response in most patients, with sustained response and steroid reduction or discontinuation in some. Treatment options for patients with steroid-refractory GVHD are limited, rituximab may be considered medically necessary in this setting.

Evidence for rituximab prophylaxis for GVHD comprises two small cohort studies, one of which included a contemporaneous control group. Although results suggested that rituximab may reduce the incidence of GVHD, replication in larger, controlled trials is needed. Due to the risk of severe adverse events with rituximab, improved health outcomes in the prophylactic setting cannot be assumed.

**Pre-Transplant Desensitization**
Rituximab has been studied in the setting of solid organ (primarily kidney) transplantation for pre-transplant desensitization, induction immunosuppressive therapy, and treatment of antibody-mediated rejection. Several cohort studies in sensitized individuals demonstrated good patient and graft survival with rituximab desensitization three years after transplant. A randomized, controlled trial (RCT) comparing desensitization regimens with and without rituximab was terminated due to excess serious adverse events in the control arm, and one study reported no
increase in polyomavirus BK-associated nephropathy at two years of follow-up. This evidence suggests that health outcomes are improved with rituximab desensitization regimens in sensitized renal transplant candidates.

**Antibody-Mediated Rejection (ABMR)**

Evidence for rituximab induction to prevent acute ABMR comprised a meta-analysis of five very low-quality trials and one 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 three years of follow-up. Rituximab has not been shown to improve health outcomes when used for induction immunosuppression in kidney transplant recipients.

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

**Practice Guidelines and Position Statements**

**Rheumatoid Arthritis**

*American College of Rheumatology (ACR)*

ACR updated its evidence-based consensus guidelines in 2012 and made the following recommendations:

- If a patient has moderate (e.g., Clinical Disease Activity Index [CDAI] >10-22 or Disease Activity Score in 28 joints [DAS-28] ≥3.2 to ≤5.1) or high (e.g., CDAI >22 or DAS-28 >5.1) disease activity after three months of MTX monotherapy or DMARD combination therapy, the panel recommended adding (Level A evidence, based on multiple RCTs) or switching (Level C evidence, based on expert consensus, case studies, or standard-of-care) to a TNF inhibitor, abatacept, or rituximab as an alternative to DMARD combination therapy.

- If a patient still has moderate or high disease activity after three months of TNF inhibitor therapy and this is due to a lack or loss of benefit, switching to another TNF inhibitor or a non-TNF biologic, such as rituximab (Level B evidence, based on a single randomized trial or nonrandomized studies), is recommended.

- Reassessment after treatment with a non-TNF biologic, such as rituximab, is recommended at six months due to anticipation that a longer time to peak effect is needed for non-TNF biologics compared with TNF inhibitors.

- Rituximab may be started or resumed in patients with RA who have a previously-treated solid malignancy, including nonmelanoma skin cancer, within the last five years, or a previously-treated melanoma skin cancer or lymphoma (Level C recommendation, based on clinical trial extensions, observational data, and expert consensus).

- The panel recommended vaccination with all killed (pneumococcal, influenza intramuscular, and hepatitis B), recombinant (human papillomavirus [HPV] vaccine for cervical cancer), and live attenuated (herpes zoster) vaccines before starting a DMARD or biologic agent.
If not administered before starting a DMARD or biologic agent, pneumococcal (killed), influenza intramuscular (killed), hepatitis B (killed), and HPV (recombinant) vaccines should be administered to RA patients already taking a DMARD or biologic agent.

Live attenuated vaccines (herpes zoster) are not recommended during therapy with biologic agents.

**European League Against Rheumatism (EULAR)**

EULAR’s 2013 recommendations for the management of RA with synthetic and biological disease-modifying anti-rheumatic drugs (DMARDs) state, “In patients responding insufficiently to MTX and/or other conventional synthetic DMARD strategies, with or without glucocorticoids, biological DMARDs (TNF inhibitors, abatacept, or tocilizumab, and, under certain circumstances, rituximab) should be commenced with MTX.” The “certain circumstances” are: recent history of lymphoma; latent tuberculosis (TB) and contraindications to chemoprophylaxis; living in a TB-endemic area; or previous demyelinating disease.

**International Consensus Expert Group**

An international (mostly European) consensus group updated its evidence-based consensus statements in 2010 and 2011. The group supported consideration of rituximab when TNF inhibitors are not suitable (Category D evidence) and in MTX-naïve patients.

**ANCA-Associated (Pauci-Immune) Glomerulonephritis**

**Kidney Diseases: Improving Global Outcomes (KDIGO)**

In 2012, KDIGO published evidence-based consensus guidelines for glomerulonephritis. Rituximab plus corticosteroid is recommended as an alternative first-line treatment (to cyclophosphamide plus corticosteroid) in patients who do not have severe disease or in whom cyclophosphamide is contraindicated (Level 1 recommendation based on level B [moderate quality] evidence).

**Idiopathic Thrombocytopenic Purpura**

**American Society of Hematology (ASH)**

In 2011, ASH published evidence-based guidelines for immune thrombocytopenia. Rituximab is suggested in the following clinical scenarios (all Grade 2 suggestions based on level C evidence [RCTs with serious flaws, weaker observational studies, or indirect evidence]):

- Children or adolescents with ITP who have significant ongoing bleeding despite treatment with IVIG, anti-RhD immunoglobulin, or conventional doses of corticosteroids.
- Children and adolescents with chronic ITP as an alternative to splenectomy or in patients who do not respond favorably to splenectomy.
- Adults with ITP who have failed one line of therapy, such as corticosteroid, IVIG, or splenectomy, and are at risk of bleeding.

**Thrombotic Thrombocytopenic Purpura**

**British Committee for Standards in Haematology (BCSH)**

BSCH published evidence-based consensus guidelines for treatment of TTP and thrombotic microangiopathy in 2012. All recommendations were based on moderate quality (Level B) evidence (based on randomized trials with important limitations or strong evidence from...
observational studies), but strength of recommendations was strong (Level 1, confidence that benefits do or do not outweigh harms). Recommendations include:

- In acute idiopathic TTP with neurological or cardiac pathology, which are associated with a high mortality, rituximab should be considered on admission, in conjunction with plasma exchange and corticosteroids (1B).
  - Ideally plasma exchange should be withheld for at least four hours after completing a rituximab infusion.
- Increased plasma exchange and/or rituximab therapy are the agents of choice in refractory or relapsing disease (1B).
- In patients in remission who have a documented reduction of ADAMTS13 activity to <5%, elective therapy with rituximab can be considered (1B).
- In resistant HIV-related TTP, rituximab could be considered (2B; weak recommendation, magnitude of benefit or not is less certain).

Multicentric Castleman Disease

**Centers for Disease Control and Prevention (CDC), the National Institutes of Health (NIH), and the HIV Medicine Association (HIVMA) of the Infectious Diseases Society of America (IDSA)**

In 2013, CDC, NIH, and HIVMA/IDSA jointly published updated evidence-based guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents. Rituximab is suggested as an optional alternative therapy for multicentric Castleman disease; regimens with ganciclovir, valganciclovir are preferred. Guideline authors noted that patients who are treated with rituximab “may experience subsequent exacerbation or emergence of Kaposi sarcoma.” (Level C [optional] recommendation based on Level 2 evidence [one or more nonrandomized trials or observational studies with long-term clinical outcomes])

**CDC, NIH, HIVMA/IDSA, the Pediatric Infectious Diseases Society (PIDS), and the American Academy of Pediatrics (AAP)**

In 2013, CDC, NIH, HIVMA/IDSA, PIDS, and AAP jointly published evidence-based guidelines for the prevention and treatment of opportunistic infections in HIV-exposed and HIV-infected children. Rituximab is not included among recommended treatments for multicentric Castleman disease.

**Multiple Sclerosis**

**American Academy of Neurology (AAN)**

AAN’s guideline on disease-modifying therapies for MS has not been reaffirmed since 2008. It does not include rituximab.

**National Institute for Health and Care Excellence (NICE)**

In April 2014, NICE issued draft guidance for the management of MS in primary and secondary care. It does not include rituximab.

**National Multiple Sclerosis Society (NMSS)**

NMSS does not include rituximab among its listed treatments for MS.
Neuromyelitis Optica  
*Neuromyelitis Optica Study Group (NMOS)*

In 2014, NEMOS published evidence-based consensus recommendations on the diagnosis and treatment of neuromyelitis optica. Rituximab is recommended as first-line treatment, along with azathioprine, and as second-line treatment after azathioprine failure.

Factor Inhibitors in Hemophilia  
*Congenital Hemophilia*  
**UK HAEMOPHILIA CENTRE DOCTORS ORGANIZATION (UKHCDO)**

In 2013, UKHCDO updated its evidence-based consensus guideline for the diagnosis and treatment of factor VIII and factor IX inhibitors in congenital hemophilia. For patients undergoing immune tolerance induction (ITI), rituximab is suggested as one of several strategies (along with FVIII dose increase; use of low-purity platelet-derived FVIII rather than recombinant FVIII; or discontinuation of ITI) if there is an inadequate decrease in inhibitor titer (<20% reduction in six months). (Grade 2 [weak] recommendation based on level C [low quality] evidence).

Acquired Hemophilia A  
**International Consensus Expert Group**

In 2009, an international group of experts in the management of acquired hemophilia published evidence-based consensus recommendations on the diagnosis and treatment of patients with acquired hemophilia A. Rituximab alone or in combination with corticosteroids is suggested as second-line therapy if first-line inhibitor eradication therapy (with corticosteroids alone or in combination with cyclophosphamide) fails or is contraindicated. (Evidence grade not provided because all recommendations and suggestions were based on low quality evidence.)

Hepatitis C Virus (HCV)-Associated Cryoglobulinemic Vasculitis  
**KDIGO**

In 2012, KDIGO published evidence-based consensus guidelines for glomerulonephritis. Rituximab in combination with IV methylprednisolone and antiviral therapy is suggested as one of several treatment options (along with plasmapheresis or cyclophosphamide, also in combination with IV methylprednisolone and antiviral therapy) for patients with HCV and mixed (IgG/IgM) cryoglobulinemia who have nephrotic proteinuria, progressive kidney disease, or an acute flare of cryoglobulinemia (Level 2 suggestion based on level D [very low quality] evidence).

Bullous Pemphigoid  
**British Association of Dermatologists (BAD)**

In 2012, BAD published evidence-based guidelines for the management of bullous pemphigoid. Rituximab received a Level D recommendation based on Level 3 evidence (case reports and case series).

Lupus Nephritis  
**American College of Rheumatology (ACR)**

In 2012, ACR published evidence-based consensus guidelines for the treatment of lupus nephritis. A task force panel voted that in some cases, rituximab can be used in patients whose
nephritis fails to improve or worsens after six months of one induction therapy, or after the patient has failed both cyclophosphamide and mycophenolate mofetil treatments (Level C evidence, based on consensus, expert opinion, or case series).

European League Against Rheumatism (EULAR) and European Renal Association-European Dialysis and Transplant Association (ERA-EDTA)
In 2012, EULAR and ERA-EDTA published joint evidence-based consensus recommendations for the management of pediatric and adult lupus nephritis. For refractory disease, i.e., for patients not responding to cyclophosphamide (CYC) or mycophenolate mofetil (MMF), treatment may be switched from MMF to CYC or from CYC to MMF, or that rituximab may be added or given as monotherapy (Category 4 evidence, based on expert committee reports or opinions and/or clinical experience of respected authorities).

KDIGO
In 2012, KDIGO published evidence-based consensus guidelines for glomerulonephritis. Rituximab is suggested as one of several treatment options (along with IVIG and calcineurin inhibitors) for patients with lupus nephritis who have failed more than one first-line regimen (Level 2 suggestion based on level D [very low quality] evidence).

Graft-Versus-Host Disease (GVHD)
British Committee for Standards in Haematology (BCSH)
In 2012, BCSH published evidence-based consensus guidelines for the diagnosis and management of acute GVHD and chronic GVHD
- Due to insufficient evidence (case reports), BCSH does not recommend rituximab for acute GVHD.
- For chronic GVHD, BCSH makes two weak recommendations (the magnitude of benefit or not is less certain):
  - Rituximab is suggested as an option for second-line treatment of refractory cutaneous or musculoskeletal GVHD (Level B evidence, based on randomized trials with important limitations or strong evidence from observational studies).
  - Rituximab may be considered for third-line treatment of chronic GVHD involving other organs (Level C evidence, based on observational studies, case series or opinion).

Consensus Conference on Clinical Practice in Chronic GVHD
In 2011, Wolff et al published evidence-based consensus guidelines on second-line treatment of chronic GVHD. Rituximab is recommended as a reasonable second-line therapy of chronic GVHD, especially in patients with sclerodermatous, lichenoid cutaneous disease, and in autoantibody-mediated cytopenias (Level C recommendation [evidence is insufficient to support for or against; use in greater than second-line treatment is justified] based on level II evidence [based on observational studies]). Evidence was insufficient to make dose recommendations.

Solid Organ Transplant
International Society of Heart and Lung Transplantation (ISHLT)
In 2012, ISHLT published evidence-based consensus guidelines for the care of heart transplant recipients. Rituximab is recommended for:
• desensitization therapy in HLA-sensitized heart transplant candidates (Class 2b recommendation, usefulness/efficacy is less well-established; level C evidence, based on expert consensus);
• in combination treatments for antibody-mediated rejection (Class 2a recommendation, weight of evidence/opinion favors usefulness/efficacy; level C evidence)

**KDIGO**
In 2009, KDIGO published evidence-based consensus guidelines for the care of kidney transplant recipients. Rituximab is discussed but not included in any recommendations. For treatment of acute rejection, guideline authors noted that “the optimal protocol to treat acute humoral rejection remains to be determined,” and RCTs comparing safety and efficacy of various regimens are lacking. IVIG plus rituximab has been used to treat recurrent (post-transplant) hemolytic-uremic syndrome that is resistant to multiple courses of plasma exchange.

**Key Words:**
Rituximab, Rituxan®

**Approved by Governing Bodies:**
Rituximab was initially approved by the U.S. Food and Drug Administration (FDA) in 1997 for the treatment of relapsed or refractory low-grade, CD20-positive, B-cell non-Hodgkin lymphoma (reviewed in Policy 2.03.05). Subsequent FDA-approved indications included rheumatoid arthritis (RA) in 2006 and GPA and MPA in 2011.

**Benefit Application:**
Coverage is subject to member’s specific benefits. Group specific policy will supersede this policy when applicable.
ITS: Home Policy provisions apply
FEP contracts: Special benefit consideration may apply. Refer to member’s benefit plan.
Lowe’s Precertification Requirement—**Effective for dates of service on or after February 1, 2010**, please contact Care Continuum at 866-240-4734 or fax the prescription with accompanying clinical information to 877-540-6223 for precertification. (This Blue Cross and Blue Shield of Alabama’s medical policy does not apply for Lowe’s members for dates of service on or after February 1, 2010. This policy was in effect for Lowe’s prior to February 1, 2010).

**Current Coding:**
HCPCS code:  
J9310 Rituximab 100 mg
References:


Policy History:
Medical Policy Administration Committee May 2002
TEC Assessment, March 5, 2002
Available for Comment May 31-July 15, 2002
Medical Policy Group, May 2005 (1)
Medical Policy Administration Committee, July 2005
Available for comment August 6-September 19, 2005
Medical Policy Group, January 2006 (1)
Medical Policy Administration Committee, January 2006
Available for comment January 28-March 13, 2006
Medical Policy Group, March 2006 (3)
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Medical Policy Group, February 2007 (1)
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Medical Policy Administration Committee, March 2007
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Medical Policy Group, February 2008 (2)
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Medical Policy Group, August 2009 (3)
Medical Policy Administration Committee, August 2009
Available for comment August 10-September 23, 2009
Medical Policy Group, February 2010 (3)
Medical Policy Administration Committee, February 2010
Medical Policy Group, January 2011
Medical Policy Administration Committee, February 2011
Available for comment February 9 – March 25, 2011
Medical Policy Group, March 2011 (1): update to Policy, Key Points and References for diagnosis of Neuromyelitis Optica
Medical Policy Administration Committee, April 2011
Available for comment April 13 – May 30, 2011
Medical Policy Group, April 2011 (1): Updated Policy, Approved by Governing Bodies and References for microscopic polyangiitis (MPA)
Medical Policy Administration Committee, May 2011
Available for comment May 11 – June 27, 2011
Medical Policy Panel, May 2011
Medical Policy Group, June 2011 (2): Updated Policy, Key Points, References
Medical Policy Administration Committee, June 2011
Available for comment, June 23 – August 31, 2011
Medical Policy Group, August 2012 (3): Update to Policy – deleted coverage for refractory multiple myeloma
Medical Policy Administration Committee, September 2012
Available for comment, September 18 through November 1, 2012
Medical Policy Administration Committee, November 2012
Available for comment, November 14 through December 28, 2012
Medical Policy Group, February 2013 (3): Clarification of policy statement diagnosis to specify primary central nervous system lymphoma (PCNSL) when standard therapies have failed as covered indication.
Medical Policy Group, March 2013 (2): Addition of marginal zone lymphoma as covered indication. Key Points and References updated to support coverage of marginal zone lymphoma.
Medical Policy Administration Committee, March 2013
Available for Comment March 12 through April 25, 2013
Medical Policy Panel, July 2014
Medical Policy Group, August 2014 (1): Removed all oncologic indications for rituximab from this policy, now on MP #475; updated Title, Description, Policy statement, Key Points and References related to addition of new coverage indications for non-oncologic uses for rituximab
Medical Policy Administration Committee, September 2014
Available for comment September 6 through October 20, 2014
This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member’s plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield’s administration of plan contracts.