Rituximab: Non-oncologic and Miscellaneous Uses

Introduction

Rituximab is a drug known as a monoclonal antibody. The drugs work with your own immune system to fight certain diseases. Rituximab attaches to and kills a certain type of immune cell known as B cells. While rituximab is often used to treat certain cancers, it also can be used for other conditions. Specifically, these conditions are those in which the B cells of the immune system incorrectly attack the body’s own healthy cells. These conditions include rheumatoid arthritis, lupus, and Wegener’s granulomatosis. This policy discusses when rituximab may be considered medically necessary.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs providers about when a service may be covered.

Policy Coverage Criteria

Note: This policy does not apply if the member has a cancer diagnosis (for these cases see policy 2.03.502 Monoclonal Antibodies for the Treatment of B-Cell Malignancies).
We will review specific intravenous (IV) and injectable drugs for medical necessity for all ages.

For those age 13 and older, we also will review the site of service for medical necessity. Site of service is defined as the location where the drug is administered, such as a hospital-based outpatient setting, an infusion center, a physician’s office, or at home.

**Drugs subject to site of service review addressed in this policy are:**

- Rituximab (Rituxan®)

**Note:** Quantity limits for individual agents can be found in Dosage and Quantity Limits section below.

---

**Click on the links below to be directed to the related medical necessity criteria:**

- Autoimmune hemolytic anemias (AIHA)
- Chronic Graft-Versus-Host Disease
- Churg-Strauss Syndrome
- Cryoglobulinemic Vasculitis Associated with Hepatitis-C Virus (HCV)
- Desensitization of Human Leukocyte Antigen (HLA)
- Hemophilia
- Idiopathic Thrombocytopenic Purpura
- Lupus Nephritis
- Microscopic Polyangiitis
- Multicentric Castleman Disease
- Neuromyelitis Optica (NMO)
- Pemphigoid Diseases
- Pemphigus Diseases
- Primary Sjögren Syndrome
- Rheumatoid Arthritis (RA)
- Site of Service
- Systemic Lupus Erythematosus (SLE)
- Systemic Sclerosis (scleroderma)
- Thrombotic Thrombocytopenic Purpura (TTP)
- Wegener’s Granulomatosis

---

<table>
<thead>
<tr>
<th>Site of Service Administration</th>
<th>Medical Necessity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medically necessary sites</td>
<td>IV infusion therapy of various medical or biologic agents will</td>
</tr>
<tr>
<td>Site of Service Administration</td>
<td>Medical Necessity</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>------------------</td>
</tr>
<tr>
<td>of service</td>
<td>be covered in the most appropriate, safe and cost effective site:</td>
</tr>
<tr>
<td>• Physician’s office</td>
<td>• These are the preferred medically necessary sites of service for specified drugs.</td>
</tr>
<tr>
<td>• Infusion center</td>
<td></td>
</tr>
<tr>
<td>• Home infusion</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hospital-based outpatient setting</th>
<th>IV infusion therapy of various medical or biologic agents will be covered in the most appropriate, safe and cost effective site:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Outpatient hospital IV infusion department</td>
<td>• This site is considered medically necessary only when the following criteria are met:</td>
</tr>
<tr>
<td>• Hospital-based outpatient clinical level of care</td>
<td>o The patient has a clinical condition which puts him or her at increased risk of complications for infusions, including any of the following:</td>
</tr>
<tr>
<td></td>
<td>▪ Known cardiac or pulmonary conditions that increase the risk of an adverse reaction</td>
</tr>
<tr>
<td></td>
<td>▪ Unstable renal function which decreases the ability to respond to fluids</td>
</tr>
<tr>
<td></td>
<td>▪ Difficult or unstable vascular access</td>
</tr>
<tr>
<td></td>
<td>▪ Acute mental status changes or cognitive conditions that impact the safety of infusion therapy</td>
</tr>
<tr>
<td></td>
<td>o The first 30 days to cover:</td>
</tr>
<tr>
<td></td>
<td>▪ The initial course of infusion of a pharmacologic or biologic agent</td>
</tr>
<tr>
<td></td>
<td>▪ Re-initiation of an agent after 6 months or longer of non-use</td>
</tr>
<tr>
<td></td>
<td>o A known history of severe adverse drug reactions and/or anaphylaxis to prior treatment with a related or similar drug</td>
</tr>
<tr>
<td></td>
<td>o There are local and regional access issues (within 50 miles) or when a hospital is the only available option for infusion of the drug</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hospital-based outpatient setting</th>
<th>These sites are considered not medically necessary for infusion and injectable therapy services of various medical and biologic agents when the site-of-service criteria in this policy are not met.</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Outpatient hospital IV infusion department</td>
<td></td>
</tr>
<tr>
<td>• Hospital-based outpatient clinical level of care</td>
<td></td>
</tr>
<tr>
<td>Condition</td>
<td>Medical Necessity</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Arthropathies</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Rheumatoid Arthritis (RA)</strong></td>
<td>Rituximab is subject to review for site of service administration.</td>
</tr>
<tr>
<td></td>
<td><strong>Rituximab may be considered medically necessary when:</strong></td>
</tr>
<tr>
<td></td>
<td>• Treating of moderately to severely active rheumatoid arthritis (eg, ≥8 swollen and ≥8 tender joints)</td>
</tr>
<tr>
<td></td>
<td>• Administered in combination with methotrexate AND</td>
</tr>
<tr>
<td></td>
<td>• Rituximab is used as a second-line therapy when either:</td>
</tr>
<tr>
<td></td>
<td>o The patient has tried and failed both adalimumab (Humira®) and etanercept (Enbrel®) tumor-necrosis factor (TNF) inhibitors.</td>
</tr>
<tr>
<td></td>
<td>OR</td>
</tr>
<tr>
<td></td>
<td>o The patient has had an inadequate response to methotrexate or other conventional synthetic disease-modifying anti-rheumatic drug (DMARD), and is not a suitable candidate for treatment with TNF inhibitors (eg, due to a recent [ie, within 5 years] history of lymphoma or other malignancy; latent tuberculosis, and contraindication to chemoprophylaxis; or previous demyelinating disease.</td>
</tr>
<tr>
<td><strong>Miscellaneous Autoimmune Diseases</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Wegener’s Granulomatosis (granulomatosis with polyangiitis)</strong></td>
<td>Rituximab is subject to review for site of service administration.</td>
</tr>
<tr>
<td><strong>Microscopic Polyangiitis</strong></td>
<td><strong>Rituximab may be considered medically necessary when:</strong></td>
</tr>
<tr>
<td></td>
<td>• Initial therapy with azathioprine, methotrexate and/or mycophenolate has been tried and failed or is contraindicated.</td>
</tr>
<tr>
<td></td>
<td>• Rituximab is used in combination with glucocorticoids.</td>
</tr>
<tr>
<td><strong>Neuromyelitis Optica (NMO)</strong></td>
<td>Rituximab is subject to review for site of service administration.</td>
</tr>
<tr>
<td></td>
<td><strong>Rituximab may be considered medically necessary when:</strong></td>
</tr>
<tr>
<td></td>
<td>• The patient is refractory to at least one standard immunosuppressive drug (eg, azathioprine or mycophenolate mofetil).</td>
</tr>
<tr>
<td>Condition</td>
<td>Medical Necessity</td>
</tr>
<tr>
<td>--------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Cryoglobulinemic Vasculitis associated with Hepatitis-C Virus (HCV)</strong></td>
<td><strong>Rituximab is subject to review for site of service administration.</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Rituximab may be considered medically necessary when:</strong></td>
</tr>
<tr>
<td></td>
<td>• Rituximab is used as add-on therapy for patients who have:</td>
</tr>
<tr>
<td></td>
<td>o Active disease resistant to anti-viral drugs</td>
</tr>
<tr>
<td></td>
<td>OR</td>
</tr>
<tr>
<td></td>
<td>o Severe or life-threatening cryoglobulinemic vasculitis</td>
</tr>
<tr>
<td><strong>Systemic Lupus Erythematosus (SLE)</strong></td>
<td><strong>Rituximab is subject to review for site of service administration.</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Rituximab may be considered medically necessary when:</strong></td>
</tr>
<tr>
<td></td>
<td>• Rituximab is used as add-on therapy for patients with the following:</td>
</tr>
<tr>
<td></td>
<td>o The patient has a confirmed diagnosis of SLE using either</td>
</tr>
<tr>
<td></td>
<td>American College of Rheumatology (ACR) or Systemic Lupus</td>
</tr>
<tr>
<td></td>
<td>International Collaborating Clinics (SLICC) criteria.</td>
</tr>
<tr>
<td></td>
<td>AND</td>
</tr>
<tr>
<td></td>
<td>o The patient has failed a 6-months trial of standard</td>
</tr>
<tr>
<td></td>
<td>induction therapy with mycophenolate, cyclophosphamide,</td>
</tr>
<tr>
<td></td>
<td>azathioprine, or other immunosuppressant, plus</td>
</tr>
<tr>
<td></td>
<td>corticosteroid.</td>
</tr>
<tr>
<td><strong>Lupus Nephritis</strong></td>
<td><strong>Rituximab is subject to review for site of service administration.</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Rituximab may be considered medically necessary when:</strong></td>
</tr>
<tr>
<td></td>
<td>• Rituximab is used as add-on therapy in patients who are</td>
</tr>
<tr>
<td></td>
<td>refractory to at least two standard first-line treatment regimens.</td>
</tr>
<tr>
<td></td>
<td>o Initial treatment has been with any two of the following:</td>
</tr>
<tr>
<td></td>
<td>▪ Cyclophosphamide, azathioprine, or other</td>
</tr>
<tr>
<td></td>
<td>▪ Immunosuppressant</td>
</tr>
<tr>
<td></td>
<td>▪ Corticosteroid (in addition to the above)</td>
</tr>
<tr>
<td><strong>Primary Sjögren Syndrome</strong></td>
<td><strong>Rituximab is subject to review for site of service administration.</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Rituximab may be considered medically necessary when:</strong></td>
</tr>
<tr>
<td></td>
<td>• Rituximab is used for patients refractory to corticosteroids and</td>
</tr>
<tr>
<td>Condition</td>
<td>Medical Necessity</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>-----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Other immunosuppressive agents</td>
<td>other immunosuppressive agents (hydroxychloroquine and/or methotrexate), then any of the following:</td>
</tr>
<tr>
<td>Systemic Sclerosis (scleroderma)</td>
<td>o Cyclophosphamide</td>
</tr>
<tr>
<td></td>
<td>o Mycophenolate</td>
</tr>
<tr>
<td></td>
<td>o Azathioprine</td>
</tr>
<tr>
<td>Systemic Sclerosis</td>
<td>Rituximab is subject to review for site of service administration.</td>
</tr>
<tr>
<td>(scleroderma)</td>
<td><strong>Rituximab may be considered medically necessary when:</strong></td>
</tr>
<tr>
<td></td>
<td>1. Rituximab is used for patients refractory to first-line treatment with cyclophosphamide or glucocorticoids.</td>
</tr>
<tr>
<td>Churg-Strauss Syndrome</td>
<td>Rituximab is subject to review for site of service administration.</td>
</tr>
<tr>
<td>(eosinophilic granulomatosis with</td>
<td><strong>Rituximab may be considered medically necessary when:</strong></td>
</tr>
<tr>
<td>polyangiitis)</td>
<td>1. Rituximab is used as first-line treatment in combination with corticosteroids for patients with severe (organ-threatening) disease.</td>
</tr>
<tr>
<td></td>
<td>2. Rituximab is used as add-on therapy for treatment-refractory disease.</td>
</tr>
<tr>
<td>Autoimmune Dermatologic Diseases</td>
<td>Rituximab is subject to review for site of service administration.</td>
</tr>
<tr>
<td>Pemphigoid Diseases:</td>
<td><strong>Rituximab may be considered medically necessary when:</strong></td>
</tr>
<tr>
<td>Bullous pemphigoid</td>
<td>1. Rituximab is used to treat refractory patients.</td>
</tr>
<tr>
<td>Mucous membrane pemphigoid</td>
<td>2. Standard initial treatment includes the following:</td>
</tr>
<tr>
<td>(including ocular cicatricial</td>
<td>o Glucocorticoids, azathioprine, mycophenolate, dapsone</td>
</tr>
<tr>
<td>pemphigoid)</td>
<td>o Second-line therapies: cyclophosphamide, rituximab and or IVIG, or extracorporeal therapies (plasmapheresis)</td>
</tr>
<tr>
<td>Epidermolysis bullosa acquisita</td>
<td><strong>Pemphigus Diseases:</strong></td>
</tr>
<tr>
<td>Pemphigus Diseases:</td>
<td></td>
</tr>
<tr>
<td>Pemphigus vulgaris</td>
<td></td>
</tr>
<tr>
<td>Pemphigus foliaceus</td>
<td></td>
</tr>
<tr>
<td>Paraneoplastic pemphigus</td>
<td></td>
</tr>
<tr>
<td>Hematologic</td>
<td>Rituximab is subject to review for site of service administration.</td>
</tr>
<tr>
<td>Autoimmune hemolytic anemias (AIHA)</td>
<td></td>
</tr>
<tr>
<td>Condition</td>
<td>Medical Necessity</td>
</tr>
<tr>
<td>------------------------------------------------</td>
<td>----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Rituximab may be considered medically necessary when:</strong></td>
<td></td>
</tr>
<tr>
<td>• Rituximab is used to treat warm AIHA in corticosteroid-refractory or corticosteroid–dependent patients.</td>
<td></td>
</tr>
<tr>
<td>• Rituximab is used to treat cold agglutination syndrome.</td>
<td></td>
</tr>
<tr>
<td>Idiopathic (immune) Thrombocytopenic Purpura</td>
<td><strong>Rituximab is subject to review for site of service administration.</strong></td>
</tr>
<tr>
<td><strong>Rituximab may be considered medically necessary when:</strong></td>
<td></td>
</tr>
<tr>
<td>• Rituximab is used in patients who do not respond to first-line treatments.</td>
<td></td>
</tr>
<tr>
<td>• In patients whose platelet counts continue to be at or less than 30,000 after first-line treatment using any one of the following:</td>
<td></td>
</tr>
<tr>
<td>o IVIg</td>
<td></td>
</tr>
<tr>
<td>o High-dose corticosteroids</td>
<td></td>
</tr>
<tr>
<td>o Anti-D immunoglobulin</td>
<td></td>
</tr>
<tr>
<td>Thrombotic Thrombocytopenic Purpura (TTP)</td>
<td><strong>Rituximab is subject to review for site of service administration.</strong></td>
</tr>
<tr>
<td><strong>Rituximab may be considered medically necessary when:</strong></td>
<td></td>
</tr>
<tr>
<td>• Rituximab is used in patients with refractory disease or relapse (i.e., lack of response to plasma exchange therapy and corticosteroids).</td>
<td></td>
</tr>
<tr>
<td>Chronic Graft-Versus-Host Disease</td>
<td><strong>Rituximab is subject to review for site of service administration.</strong></td>
</tr>
<tr>
<td><strong>Rituximab may be considered medically necessary when:</strong></td>
<td></td>
</tr>
<tr>
<td>• Rituximab is used in patients refractory to corticosteroids.</td>
<td></td>
</tr>
<tr>
<td>Desensitization of human Leukocyte Antigen (HLA)</td>
<td><strong>Rituximab is subject to review for site of service administration.</strong></td>
</tr>
<tr>
<td><strong>Rituximab may be considered medically necessary when:</strong></td>
<td></td>
</tr>
<tr>
<td>• Rituximab is to be used in HLA-sensitized renal transplant candidates before transplantation.</td>
<td></td>
</tr>
<tr>
<td>Hemophilia</td>
<td><strong>Rituximab is subject to review for site of service administration.</strong></td>
</tr>
</tbody>
</table>
### Condition

**Medical Necessity**

**Rituximab may be considered medically necessary when:**
- Rituximab is used as a factor inhibitor for patients who are refractory to conventional first-line treatments (e.g., immune tolerance induction, corticosteroids with or without cyclophosphamide).

**AND**
- Rituximab is used as add-on therapy (reviewed on a case-by-case basis).

### Other

**Multicentric Castleman Disease**

**Rituximab is subject to review for site of service administration.**

**Rituximab may be considered medically necessary when:**
- Rituximab is used in patients with or without chemotherapy.

**Note:** Treatment in the context of a clinical trial is encouraged.

### Drug

**Investigational**

**Rituximab (Rituxan®)**

**Rituximab is investigational for all other non-oncologic uses, including but not limited to:**
- Paroxysmal cold hemoglobinuria
- Mixed connective tissue disease (MCTD)
- Multiple sclerosis
- Prophylaxis for graft-versus-host disease
- Induction immunosuppressive therapy for solid organ transplantation
- Treatment of antibody-mediated rejection (ABMR) in solid organ transplant recipients
- Treatment of ABMR after pancreatic islet transplantation

**All other uses of rituximab for conditions not outlined in this policy are considered investigational.**

**Note:** Quantity limits for individual agents can be found in the Dosage and Quantity Limits section below.
Dosage and Quantity Limits

<table>
<thead>
<tr>
<th>Condition</th>
<th>Dosage and Quantity Limit of Rituximab (Rituxan®)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid arthritis</td>
<td>• In combination with methotrexate, dosing is two 100 mg IV infusions, separated by 2 weeks (one course) every 24 weeks or based on clinical evaluation but no sooner than every 16 weeks.</td>
</tr>
<tr>
<td>Wegener’s granulomatosis (granulomatosis with polyangiitis)</td>
<td>• In combination with glucocorticoids, dosing is 375 mg / m² once weekly for 4 weeks.</td>
</tr>
<tr>
<td>For all other indications</td>
<td>• There is no dosing information provided in the package insert.</td>
</tr>
</tbody>
</table>

Coding

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCPCS</td>
<td></td>
</tr>
<tr>
<td>J3490</td>
<td>Unclassified drugs</td>
</tr>
<tr>
<td>J3590</td>
<td>Unclassified biologics</td>
</tr>
<tr>
<td>J9310</td>
<td>Injection, rituximab, 100 mcg (Rituxan®, generic rituximab)</td>
</tr>
</tbody>
</table>

Related Information

Dosing

Rituximab should be administered by a healthcare professional with appropriate medical support to manage severe and potentially fatal infusion reactions.

Rheumatoid Arthritis

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

Although a 2014 systematic review with meta-analysis reported no statistical difference in clinical and patient-reported outcomes at 24 and 48 weeks with 500 mg doses of rituximab, radiographic outcomes were not assessed.\(^2\) A pivotal trial showed radiographic improvements compared with placebo in patients receiving rituximab 1000 mg, but not in patients receiving rituximab 500 mg.

**Granulomatosis with Polyangiitis (Wegener Granulomatosis) and Microscopic Polyangiitis**

Rituximab 375 mg/m\(^2\) is administered weekly for 4 weeks, in combination with glucocorticoids. Pneumocystis jiroveci pneumonia (PCP) prophylaxis is recommended during treatment and for at least 6 months following the last rituximab infusion.

**Adverse Events**

Rituximab carries the following black box warnings\(^1\):

- Fatal infusion reactions within 24 hours of rituximab infusion; approximately 80% of fatal reactions occurred with first infusion.
- Severe mucocutaneous reactions, some with fatal outcomes
- Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, and death
- Progressive multifocal leukoencephalopathy (PML) resulting in death

Labelled warnings and precautions include:

- Tumor lysis syndrome (for patients with hematologic malignancies)
- Infections
- Cardiac arrhythmias and angina
• Bowel obstruction and perforation

• Live virus vaccines: Do not administer live virus vaccines before or during rituximab therapy

• Cytopenias

Adverse events that occurred in at least 10% of patients in pivotal rheumatoid arthritis trials included upper respiratory tract infection, nasopharyngitis, urinary tract infection, and bronchitis.

Adverse events that occurred in at least 15% of patients in the pivotal Wegener granulomatosis and microscopic polyangiitis study included infections, nausea, diarrhea, headache, muscle spasms, anemia, and peripheral edema.

Pregnancy

Rituximab is pregnancy category C: There are no adequate and well-controlled studies of rituximab in pregnant women. Women of childbearing potential should use effective contraception while receiving rituximab and for 12 months after treatment. Rituximab may be used during pregnancy only if potential benefit justifies potential risks to the fetus.

Children

The age described in this policy for medical necessity of select intravenous and injectable therapy services is 13 years of age or older. The age criterion is based on the following: Pediatric patients are not small adults. Pediatric patients differ physiologically, developmentally, cognitively, and emotionally from adult patients, and vary by age groups from infancy to teen. Children often require smaller doses than adults, lower infusion rates, appropriately sized equipment, the right venipuncture site determined by therapy and age, and behavioral management during administration of care. Specialty infusion training is therefore necessary for pediatric IV insertions and therapy. Due to pediatrics unique physiology and psychology, this policy is limited to patients above the age of 13.

Evidence Review

U.S. Food and Drug Administration–Approved Uses
Rheumatoid Arthritis

Rituximab is U.S. Food and Drug Administration (FDA)-approved in combination with methotrexate (MTX) to reduce signs and symptoms of moderately- to severely-active rheumatoid arthritis (RA) in adults who have had an inadequate response to at least 1 tumor necrosis factor (TNF) inhibitor. Use in patients with RA who have not had a previous inadequate response to 1 or more TNF inhibitors is not recommended.¹

FDA approval of rituximab for RA was based on 4 placebo-controlled, randomized trials.¹ 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 1 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, ACR70, respectively]) compared with patients who received placebo.⁴ 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 2 courses of rituximab approximately 6 months apart had improved outcomes at 48 weeks (as assessed by ACR20) compared with those who received only 1 course of rituximab.⁵ 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.¹

A fourth randomized controlled trial (RCT) (IMAGE) compared rituximab 500 mg with 1000 mg dosing in MTX-naïve patients.³ All patients received MTX. 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, 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.¹

Other studies have confirmed improvements in ACR20, ACR50, and ACR70 in patients treated with rituximab plus MTX compared with placebo plus MTX (summarized by Thaler et al [2012]).⁶ Keystone et al. (2012) reported 5-year follow-up of the pivotal REFLEX trial.⁷ Patients initially randomized to the placebo arm could receive rituximab in an observational extension study.
400 patients who received 1 course of rituximab, ACR20, ACR50, and ACR70 responses were 62%, 31%, and 13%, respectively. In 91 patients who received 5 courses of rituximab, responses were 70%, 42%, and 22%, respectively. In 184 patients who had baseline and 5-year radiographs available, progression of joint damage over 5 years was less in rituximab-treated than in placebo-treated patients, although this difference was not statistically significant. Adverse event (AE) rates were generally stable over 5 years of follow-up.

Section Summary

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

Wegener Granulomatosis (Granulomatosis with Polyangiitis) and Microscopic Polyangiitis

Wegener granulomatosis (granulomatosis with polyangiitis [GPA]), microscopic polyangiitis (MPA), and Churg-Strauss syndrome are classified as antineutrophil cytoplasmic antibody (ANCA)–associated vasculitides because most patients with generalized disease have antibodies against proteinase3 (PR3) or myeloperoxidase (MPO), enzymes found in neutrophil granulocytes.8 Each vasculitis can be distinguished by the predominant type of immunofluorescence staining pattern (antibody) present, eg, 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.9 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.10 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 1 active-controlled, RCT, the Rituximab in ANCA-Associated Vasculitis (RAVE) noninferiority trial.\(^8\) Patients 15 years of age or older who had severe (Birmingham Vasculitis Activity Score for Granulomatosis with Polyangiitis [BVAS/GPA] ≥3 [scores range, 0-63, with higher scores indicating more active disease], with at least 1 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 6 years. Patients were randomized to receive rituximab 375 mg/m\(^2\) weekly for 4 weeks (remission induction phase) followed by oral placebo beginning at 3 to 6 months (maintenance phase; n=99), or cyclophosphamide 2 mg/kg orally daily for 3 to 6 months (remission induction) followed by oral azathioprine daily beginning at 3 to 6 months (maintenance phase; n=98). All patients received 1 to 3 pulse doses of parenteral methylprednisolone 1000 mg followed by prednisone 1 mg/kg orally daily. Patients who achieved remission tapered and discontinued prednisone by month 5. The primary end point was complete remission at 6 months, defined as BVAS/GPA of 0 off prednisone. The prespecified noninferiority margin was a treatment difference of -20 percentage points (rituximab group minus cyclophosphamide group). At 6 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 AEs 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 group (8% vs 2% cyclophosphamide).

Specks et al. (2013) published 18-month follow-up results.\(^11\) 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 to 12 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, 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. (2010) 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).\(^12\) 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; 9 patients were dialysis-dependent (GFR=0). Patients were randomized 3:1 to rituximab 375 mg/m² weekly for 4 weeks plus IV cyclophosphamide 15 mg/kg with the first and third rituximab infusions, or IV cyclophosphamide for 3 to 6 months followed by azathioprine. Both groups received 1 dose of methylprednisolone 1 g IV and oral corticosteroid 1 mg/kg daily reducing to 5 mg daily at the end of 6 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 9 patients in the control group (82%) had a sustained remission (x² test, p=0.68). SAEs occurred in 14 patients in the rituximab group (42%) and 4 patients in the control group (36%; x² test, p=0.77); 2 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, 91-100) 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, p=0.14). Six of 8 dialysis-dependent patients randomized to rituximab had a sustained remission, 5 of whom no longer required dialysis; 1 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, 6 (18%) of 33 patients in the rituximab group and 3 (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 GPA (formerly called Wegener granulomatosis) or 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 SAEs at 12 months in patients treated with or without a rituximab-containing induction regimen.
Off-Label Uses

Autoimmune Blood Disorders

Autoimmune Hemolytic Anemia

Autoimmune hemolytic anemia (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 reacts optimally with human red blood cells in vitro at 37°C (98.6°F). Cold-reactive antibodies, primarily IgM, react maximally at 4°C (39°F). Cold AIHA in turn comprises cold agglutinin syndrome and paroxysmal cold hemoglobinuria. Warm and cold AIHA may be idiopathic (primary) or secondary, eg, to lymphoma or lymphoproliferative disorders. Corticosteroids are first-line treatment in warm AIHA but less effective in cold AIHA.13,14

Warm AIHA

A 2011 systematic review of treatments for idiopathic warm AIHA in adults identified 3 studies (case series) of rituximab treatment for refractory disease (total N=42).15 Overall response rate was 93% (complete response [CR], 43%; partial response [PR], 50%). One study reported relapse in 2 (15%) of 13 responders and severe sepsis in 1 (4%) of 27 rituximab-treated patients with a mean follow-up of 21 months.16 The authors of the systematic review recommended rituximab 375 mg/m2 weekly for 4 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.17 Patients were randomized to rituximab (375 mg/m2 weekly for 4 weeks) plus short-course (2 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 (p=0.003). At 36 months, 70% of rituximab responders and 45% of control responders maintained CR or PR (log-rank test, p=0.02). SAEs occurred in 9 (28%) of 32 rituximab-treated patients and 5 (17%) of 32 controls (Fisher exact test, p=0.12). These included 5 serious infections in the rituximab group and 2 serious infections in controls (Fisher exact test, p=0.16).
Cold Agglutinin Syndrome

In a 2008 review of cold AIHA, Petz identified 11 case reports and case series of rituximab in cold agglutinin syndrome (CAS). In 2 case series (total N=47), overall response rate was 62%. Median duration of response in 20 responders was 11 months, and no SAEs 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.

Paroxysmal Cold Hemoglobinuria

Due to the generally self-limiting course and excellent prognosis of paroxysmal cold hemoglobinuria, rituximab is not considered a treatment option.

Idiopathic Thrombocytopenic Purpura

Idiopathic thrombocytopenic purpura (ITP) is an acquired autoimmune disorder with no known cause, although it can co-occur with other autoimmune diseases. Corticosteroids, IV immunoglobulins (IVIG), or anti-Rho(D) immunoglobulin are standard initial treatments. 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 4 RCTs were included (total N=368 nonsplenectomized patients). Publication bias was not detected. Thirteen studies dosed rituximab at 375 mg/m2 weekly for 4 weeks; 6 studies used alternative regimens. Concomitant medications were not described. Median follow-up was 9 months (range, 2.3-65). Pooled overall response rate (platelet count, >50x10⁹/L) was 57% (95% CI: 48 to 65; I²=49%; 20 studies), and 57% (95% CI: 35 to 76; I²=79%) at 1 year (6 studies). In separate analyses, CR rate (defined as platelet count either >150x10⁹/L or >100x10⁹/L) was 41% (95% CI: 33 to 50; I²=51%; 19 studies) and 40% (95% CI: 31 to 49; I²=0%) at 1 year (5 studies). 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. AEs 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 8 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/m² weekly for 4 doses; concomitant medications were not described. Pooled overall response rate (platelet count, ≥30x10⁹/L with at least doubling of the platelet count, a standard response criterion) was 68% (95% CI: 58 to 77; I²=68%), and pooled CR (platelet count, ≥100x10⁹/L) was 39% (95% CI: 30 to 49; I²=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, 4.5-25.1). Incidence of grade 3 to 4 infection and grade 3 to 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/m² weekly for 4 weeks plus dexamethasone 40 mg daily for 4 days (n=62) or dexamethasone alone (n=72). Patients had baseline platelet counts of 25x10⁹/L or less, or 50x10⁹/L or less with bleeding symptoms. Median follow-up was 2.5 years. Overall response rate (platelets count ≥50x10⁹/L) sustained at 6 months was 58% in the rituximab group and 37% in the control group (Fisher exact test, p=0.02); at 12 months, sustained response rate was 53% and 33%, respectively (Fisher 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 15x10⁹/L (IQR, 7-24). Time to relapse also was longer in the rituximab group (log-rank test, p=0.03). SAEs occurred more commonly in the rituximab group than in the control group (26% vs. 11%; Fisher exact test, p=0.04). Because the authors reported numbers of AEs rather than patients who experienced AEs, 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/m² weekly for 4 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 50x10⁹/L, significant bleeding, or rescue treatment once standard treatment was stopped. At 6 months, the between-group difference of the composite end point was not statistically significant (64% rituximab vs 78% placebo; relative risk, 0.81; 95% CI: 0.59 to 1.11). Differences in overall (platelet count, ≥30x10⁹/L) or complete (platelet count, ≥100x10⁹/L) response were not statistically significant at 6 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 SAEs were comparable between groups. Because numbers of AEs rather than patients who experienced AEs were reported, incidences could not be calculated.
Thrombotic Thrombocytopenic Purpura

Thrombotic thrombocytopenic purpura (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, 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% to 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. The mainstay of treatment for TTP is plasma exchange (PE) and corticosteroids. Refractory TTP, defined as progression of clinical symptoms during PE therapy, occurs in 10% to 20% of acquired TTP cases. For these patients, increased PE and/or addition of cyclosporine are current treatment options.

Evidence for rituximab in TTP comprised 1 phase 2 cohort study and several case series. All studies enrolled patients with acquired (ie, anti-ADAMTS13 antibody-positive) TTP.

Relapsed or Refractory TTP

Scully et al. (2011) conducted a Phase II, 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 4 weeks; 3 patients died and 1 withdrew before receiving all 4 doses of rituximab. All patients and historical controls received PE at admission and then daily (or twice daily for new or progressive neurologic or cardiac symptoms; protocol maximum of 8 infusions) until remission, defined as sustained platelet count (>15x10^9/L) for 2 consecutive days; corticosteroid (typically methylprednisolone 1 g IV daily) was given for 3 days. The primary efficacy outcome was the number of PE treatments to remission. Forty enrolled patients received a median of 16.5 (range, 4-34) PE 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 (4 in the rituximab group, 21 in the control group), median time to relapse (defined as readmission with thrombocytopenia less than 150x10^9/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. Incidence of infections and SAEs was similar between groups.
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.\textsuperscript{27} Patients received methylprednisolone daily for 3 days, daily PE until sustained platelet count (previously defined as), and rituximab 375 mg/m\textsuperscript{2} immediately after PE weekly for 4 weeks. All 25 patients achieved clinical remission (defined as cessation of PE, sustained platelet count, and absence of clinical disease) within 1 to 3 weeks of treatment. During median follow-up of 10 months (range, 1-33), there were no relapses and no infectious complications.

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.\textsuperscript{22} Studies of secondary TTP and empirical rituximab treatment were excluded. In all studies, rituximab was dosed at 375 mg/m\textsuperscript{2} weekly for a median of 4 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, \textless \text{10\%}) predicted response to rituximab (positive predictive value, 99\% for both). Serious rituximab-related AEs occurred in 3 patients (3\%): acute biventricular cardiogenic shock, sacral abscess, and abdominal abscess.

**TTP Prophylaxis**

Fakhouri et al. (2005) reported on 5 patients with highly recurrent (4-15 episodes) TTP who were not experiencing an acute TTP relapse.\textsuperscript{28} Patients received prophylactic rituximab 375 mg/m\textsuperscript{2} weekly for 4 weeks. Although patients were in clinical remission, all had undetectable ADAMTS13 activity, suggesting susceptibility to relapse. At 3, 6, and 9 months, 80\%, 100\%, and 80\% achieved clinical remission, defined as recovery of ADAMTS13 activity to more than 10\% and no detectable circulating anti-ADAMTS13 antibody.

**Section Summary**

Evidence for rituximab in AIHA comprises a small number of patients with primary (idiopathic) and secondary disease. For warm AIHA, case series and case reports describe patients with refractory disease, and an RCT enrolled patients with previously untreated disease. Response rates were 75\% to 93\%; sustained responses to 3 years were observed; relapses occurred in 5\% to 15\% of patients. Serious infections were observed in 4\% to 15\% of patients. For 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, 8 years], 1 in adults) and 2 RCTs in adults investigated mostly non-splenectomized patients. Overall and CR rates were approximately 57% and 40%, respectively, in adults, and 68% and 39% in children. Median response durations were approximately 1 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. AE 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 ITP who do not respond to first-line treatments and are able to delay or avoid splenectomy with rituximab treatment.

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

**Churg-Strauss Syndrome (Eosinophilic Granulomatosis with Polyangiitis)**

Churg-Strauss syndrome, also called eosinophilic granulomatosis with polyangiitis, is an ANCA-associated vasculitis characterized by peripheral and tissue eosinophilia, frequently affecting the lungs, in patients with asthma. Eosinophilic infiltration of the heart, lungs, and kidneys can lead to ventricular dysfunction, pulmonary hemorrhage, and renal failure, respectively; cardiac involvement is the leading cause of early death. Treatment recommendations are based primarily on studies in other ANCA-associated vasculitides (GPA and MPA). Corticosteroids are
used with or without cyclophosphamide, depending on disease severity. Azathioprine or MTX may be used as steroid-sparing agents. Because of its demonstrated efficacy in GPA and MPA, rituximab has been used in patients with Churg-Strauss syndrome refractory to conventional immunosuppressant therapy.\textsuperscript{30}

Thiel et al. (2013) reported the largest case series of 9 treatment-refractory patients who received rituximab add-on therapy.\textsuperscript{31} All patients responded (1 CR [Birmingham Vasculitis Activity Score, BVAS=0 for ≥3 months and stable prednisone dose ≤7.5 mg daily], 8 partial remissions [BVAS >0]) after 1 cycle of rituximab with no relapses in 9 months of follow-up. Three patients who received preemptive retreatment (ie, not in response to relapse) were relapse-free for a median follow-up of 3 years. Five (55\%) of 9 patients had minor respiratory infections. One patient who received a second (preemptive) course of rituximab developed a testicular seminoma 12 months after the first cycle (6 months after the second cycle).

**Section Summary**

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

**Factor Inhibitors in Hemophilia**

Hemophilia is a coagulopathy characterized by reduced, absent, or nonfunctioning 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\% to 30\% of patients with severe hemophilia A and 2\% to 5\% of patients with hemophilia B.\textsuperscript{32} If left untreated, antibody inhibitors eventually render replacement therapy ineffective. Immune tolerance induction (ITI) is recommended first-line treatment of factor inhibitors in hemophilia.\textsuperscript{33} 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 (eg, 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 the studies administered rituximab in combination with ITI or other immunosuppressive treatment (eg, 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 AEs were reported. In multivariate analysis, coadministration with factor VIII ITI was statistically associated with response (hazard ratio [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-Kuhne 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 AEs 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 ITI-refractory patients with congenital hemophilia and factor inhibitor, complete remission occurred in 53% of patients who received rituximab alone or in combination with continued ITI; a small cohort study supported combination therapy in the refractory setting. A comparative study in acquired hemophilia A did not find improved response rates in patients treated with rituximab alone or in combination compared with standard cyclophosphamide plus cyclosporine. Evidence does not support rituximab as an alternative to standard treatments for factor inhibitor eradication (ie, ITI in congenital hemophilia and immunosuppression with cyclophosphamide and corticosteroids in acquired hemophilia A). However, evidence suggests that patients who are refractory to these first-line treatments may benefit from rituximab without an increase in AEs. Combination regimens may be preferred. Given the lack of treatment options in refractory patients and the serious, possibly fatal, outcomes if factor inhibitors are not eradicated, rituximab may be considered medically necessary in this setting.

Hepatitis C Virus–associated Cryoglobulinemic Vasculitis

Of 3 types of cryoglobulinemia, type 2 and type 3 may be called “mixed” due to the clonal expansion of more than 1 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 hepatitis C virus (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.36,37

In 2013, Dammacco et al.37 and Puéchal et al.38 published reviews of HCV-associated cryoglobulinemic vasculitis. Previous treatment recommendations39 recently published RCTs, (40,41) and heterogeneous nonrandomized studies (that varied in design, HCV genotype, previous treatment, rituximab dose, concomitant therapy) (total N=377 patients) reported response rates of approximately 80%, and led the reviewers to draw the following conclusions37,38.
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.

- For patients with mild-to-moderate disease activity, antiviral therapy is recommended as first-line treatment.
- 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.
- Pegylated interferon alfa may exacerbate some clinical features of cryoglobulinemic vasculitis, such as skin ulcers and peripheral neuropathy.
- 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 4 weekly infusions of 375 mg/m2.

- 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 HCV-associated cryoglobulinemic vasculitis. Across 2 RCTS and many observational studies (total N=377), median overall response was approximately 80%. However, these studies were done before the advent of several new HCV antiviral drugs and pegylated interferon–free drug regimens. More effective antiviral treatments should improve outcomes, 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

Mixed connective tissue disease (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 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 3 years. Patients were treated with rituximab and followed for at least 6 months. Five patients were considered to have a mixed connective tissue disorder, 2 unclassified, 1 Sjögren syndrome, and 2 MCTD. One death 3 months after starting rituximab in a patient with a mixed connective tissue disorder was attributed to disease progression. Of the 4 remaining patients with a mixed connective tissue disorder, 3 attained partial remission, and 1 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 5 patients with MCTDs, 3 of whom achieved partial remission with rituximab, is insufficient to determine the efficacy and safety of rituximab for the treatment of MCTD.

Multicentric Castleman Disease

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 2 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 1 prospective and 2 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 2-year overall survival (OS) was 95%. Of 11 patients who had Kaposi sarcoma at baseline, progression occurred in 4 (36%). No grade 3-4 AEs 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, 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 4 (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 1 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 (HR=0.09; 95% CI: 0.01 to 0.70). Two- and 5-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 1 newly diagnosed Kaposi sarcoma were observed in 9 patients after rituximab therapy. Among 36 rituximab responders, multicentric Castleman disease recurred in 8 (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, 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. CR occurred in 5 patients (81%).

One case report of rituximab in multicentric Castleman disease in an HIV-uninfected patient was identified. Complete remission was achieved after 4 cycles of rituximab and followed by 4 months of corticosteroid maintenance therapy. Recurrence was not detected during more than 4 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 NHL and substantially improved OS (≥93% at 2 years in 2 studies; 90% at 5 years in 1 study) in rituximab-treated patients compared with non-rituximab-treated unmatched controls. Progression or emergence of Kaposi sarcoma is an associated risk of rituximab treatment, with Kaposi sarcoma recurrence in approximately 30% of patients. No studies comparing rituximab with currently-suggested first-line treatment with ganciclovir or valganciclovir were identified. However, given the low-quality evidence supporting this recommendation and aggressive course of multicentric Castleman disease, effective treatment with rituximab may outweigh its associated risks. Therefore, rituximab may be considered medically necessary for multicentric Castleman disease in the first- or second-line setting.

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 posttreatment) and improvements in EDSS, except in severely disabled patients (e.g., baseline EDSS=8.7) for whom neurologic damage may be irreversible. Dosing regimen was commonly 375 mg/m² followed by 1000 mg biweekly for 2 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 1 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, 1 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, interferon, glatiramer acetate, and IVIG.

**Section Summary**

Evidence for rituximab in 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., interferon and glatiramer acetate), efficacy of rituximab appeared comparable with that of azathioprine and MMF, considered first-line immunosuppressive drugs for NMO. Based on AEs 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 8 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 3 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 (4 epidermolysis bullosa acquisita, 1 bullous pemphigoid) and pemphigus diseases (52 pemphigus vulgaris, including 1 pemphigus vegetans, a localized form of pemphigus vulgaris, 9 pemphigus foliaceus, and 5 paraneoplastic pemphigus). Fifteen (21%) of 71 patients received rituximab monotherapy; 56 (79%) received concomitant systemic corticosteroids, immunosuppressive drugs, and/or IVIG. Overall, 49 patients (69%) had a CR, 18 (25%) had a PR, and 4 (6%) had progressive disease (2 patients with paraneoplastic pemphigus, 1 with pemphigus foliaceus, and 1 with pemphigus vegetans). Of 6 deaths associated with rituximab, 4 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 1 death occurred in a patient with bullous pemphigoid and graft-versus-host disease (GVHD) who developed sepsis. Infections (pneumonia and infective arthritis) also were reported in 2 other patients with pemphigus vulgaris who received rituximab in combination with corticosteroids and immunosuppressive drugs. Overall incidence of infections was 7%. Noninfectious AEs 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 AEs 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 (1 case series, 8 case reports), including 4 children, (mean age, 6.4 years; range, 5 months to 14 years) were identified. Fourteen patients (88%) received rituximab 375 mg/m² weekly for 4 doses, and 2 patients (12%) received 1000 mg IV every other week for 2 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, 1 (6%) had a PR, 1 (6%) had no response, and 3 (19%) died. Deaths were due to sepsis in 2 patients (1 child) and cardiac AEs. 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 4 weeks were included. Twenty-eight patients (1 case series, 6 case reports) were identified. Median follow-up ranged from 9 to 31 months. All patients received concomitant immunosuppressive and/or immunoadsorbent therapy. Twenty (71%) of 28 patients had a CR, 3 (11%) had a PR, 2 (7%) were nonresponders, and 1 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 1 eye. Six patients received rituximab 375 mg/m² weekly for 8 weeks plus IVIG, and 6 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 6 control patients had progressed to blindness in both eyes. No AEs 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 2 weeks for 2 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 6 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, 8-64 months), each of whom received an additional infusion of rituximab 500 mg IV and achieved a CR. No SAEs were observed.

Section Summary

Evidence for rituximab in pemphigoid and pemphigus diseases comprises case reports, case series, and 1 retrospective comparative study in ocular cicatricial pemphigoid. Patients were refractory to previous treatments, but most (75%-100%) responded to rituximab. Infections, including serious and fatal infections, were reported in 4% to 19% of patients, but AE reporting may have been incomplete. Only 3 of 8 pemphigoid diseases were examined in the literature: epidermolysis bullosa acquisita, bullous pemphigoid, and mucous membrane pemphigoid. Although the body of evidence is small, disease progression can lead to serious outcomes (eg, blindness) or death, reported response rates were high, and treatment options in refractory patients are limited. For these reasons, rituximab may be considered medically necessary for treatment of the pemphigoid and pemphigus diseases reviewed in the literature in treatment-refractory patients.

Primary Sjögren Syndrome

Sjögren 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. Sjögren syndrome often accompanies other autoimmune disorders, such as RA 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 Sjögren syndrome. Literature was searched through April 2010, and 2 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 2 doses, although other symptoms, eg, 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 Sjögren syndrome and at least 1 extraglandular manifestation to rituximab 1000 mg weekly for 2 doses or placebo, and assessed response in global disease, pain, fatigue, and dryness at 24 weeks. Mean (SD) baseline European Sjögren Syndrome Disease Activity Index (ESSDAI, a validated 0 [no symptoms] to 49 [high disease activity] scale of systemic disease activity in patients with Sjögren syndrome) score was 10. Baseline corticosteroids (30% of patients) and MTX (20% of patients) were discontinued 4 weeks before trial entry. By prespecified response criteria (≥30 mm improvement in 2 of 4 symptom visual analog scales at week 24), a statistically significant between-group difference was not observed. A statistically significant difference in proportion of responders was observed at 6 weeks and in reduction of fatigue at 6 and 16 weeks, both favoring rituximab. Serious infection occurred in 3% of rituximab-treated patients and 9% of controls, but overall SAEs 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 (6 courses at 6-month intervals of rituximab 1000 mg biweekly for 2 doses; n=19) with conventional disease-modifying antirheumatic drugs (DMARDs [hydroxychloroquine, MTX, or cyclosporine]; n=22) in patients with early-onset primary Sjögren syndrome. A minimum ESSDAI score of 6 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 6 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 2 registry studies of patients with primary Sjögren 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 (eg, MS-like symptoms [n=6], cognitive dysfunction [n=3]), only 1 patient with cyclophosphamide-refractory transverse myelitis reported improvement in ability to walk, and 1 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 neurologic improvements occurred in 11 patients (65%) at 3 months and persisted in 9 patients (53%) at 6 months. Statistically significant improvements in objective measures (Rankin scale, a 0 [no symptoms] to 6 [dead] scale of overall neurologic function, and ESSDAI) were observed at 3, 6, and 9 months. Physician-assessed improvements at 3 months and change in ESSDAI at 6 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 1 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 5 patients (6%). Three serious infections (1.3/100 patient-years) and 2 cancer-related deaths occurred.

Section Summary

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

Systemic Lupus Erythematosus

One RCT, EXPLORER, and several systematic reviews were identified. A 2014 systematic review examined several biologic agents and included only 2 rituximab trials, EXPLORER and LUNAR, which are described next. Three systematic reviews that included the EXPLORER trial are summarized in Table 1. 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. (2013) 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 1. Systematic Reviews of Rituximab in Systemic Lupus Erythematosus

<table>
<thead>
<tr>
<th>Study</th>
<th>N/n</th>
<th>Follow-up, mo</th>
<th>Efficacy</th>
<th>Adverse Eventsa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cobo-Ibanez (2014)</td>
<td>25b (1 RCT)/1231</td>
<td>Range, 2-103</td>
<td>CR/PR: 64%-91% TTR: 4-18 mo.</td>
<td>Serious infections: 7%-13%</td>
</tr>
<tr>
<td>Duxbury (2013)</td>
<td>30 (3 RCTsc)/1243</td>
<td>Range, 2-38</td>
<td>PR: 31%-38% CR: 47%-57%</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% CR: 33% TTR 3-44 mo</td>
<td>Severe allergic reactions: 10%</td>
</tr>
</tbody>
</table>

CR: complete response; N/n: number of studies/number of patients; PR: partial response; RCT: randomized controlled trial; 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 systemic lupus erythematosus.

The 2010 EXPLORER (Exploratory Phase II/III 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 MTX. At 1-year 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) was 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 PRs (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 replication. Safety and tolerability were
similar in both groups. In 2011, the authors reported a post hoc analysis using alternative definitions of flare in the 72% of patients (N=185) who achieved low disease activity (BILAG C or better) at any point before week 52.\textsuperscript{88} When mild (BILAG A) flares alone were examined, rituximab reduced the risk of a subsequent BILAG A flare and the mean annualized rate of BILAG A flares.

A letter about this trial suggested that the stringent end point used in EXPLORER—improvement to BILAG C in all organs—may have been unrealistic.\textsuperscript{89} Based on observational data, rituximab appears to improve renal and musculoskeletal symptoms more than neurologic, cutaneous, and cytopenic symptoms in SLE patients; organ-specific improvements may have been informative end points. Similarly, change in corticosteroid dose may have demonstrated a steroid-sparing effect with rituximab. Additionally, possible differences in dosages of background immunosuppressive therapies (not reported) may have biased results.

\textit{Lupus Nephritis}

Lupus nephritis (LN) is among the most serious complications of SLE. It occurs in approximately half of SLE patients and is associated with a poor prognosis.\textsuperscript{90} Estimated 5-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%\textsuperscript{91}; 5% to 10% of LN patients will progress to end-stage renal disease at 10 years.\textsuperscript{92} Current treatment regimens include cyclophosphamide or MMF, both administered with corticosteroids. Response rates at 1 year are approximately 50% to 80%, but these are often only partial responses.\textsuperscript{90}

Evidence for the use of rituximab in LN comprised 1 systematic review, 1 RCT, 1 registry study, and several case series and case reports.

A 2013 systematic review of rituximab in refractory LN included 9 prospective comparative studies, 9 retrospective studies, and 8 case series and case reports (total N=300).\textsuperscript{93} 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 MTX) varied across studies; the most common dosing regimen was 375 mg/m\textsuperscript{2} weekly for 4 weeks. Mean follow-up was 60 weeks (range, 12-120). Rituximab induced a CR, PR, 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. CRs and any responses (CR or PR) 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 previously described was the 2012 double-blind LUNAR trial (Lupus Nephritis Assessment with Rituximab). LUNAR was a randomized, double-blind, placebo-controlled Phase III 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 overall (CR or PR) renal response rate at 1 year with rituximab, was not reached (57% [26% CR, 31% PR] in the rituximab group vs. 46% [31%CR, 15% PR] in the placebo group; 2 test, p=0.18). Incidence of SAEs did not differ statistically between groups. An accompanying editorial observed that the trial was powered to detect a 20% increase in complete renal response and a 5% increase in partial renal response; it was underpowered to detect a difference comprising mainly partial responses.

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, 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 6 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 (CR or PR) responses were more common in patients with class III LN than in patients with class IV or class V LN (x2 test, p=0.007 and 0.03, respectively). Two patients (1%) developed severe infusion reactions. Twenty patients (12%) had 21 infections: 7 respiratory infections (4 pneumonia, 3 respiratory tract infections), 5 sepsis, 2 urinary tract infections, 2 osteoarticular infections (1 septic arthritis, 1 necrotizing fasciitis), 4 viral infections (3 herpes zoster, 1 CMV viremia), and 1 pneumococcal meningitis. Six patients (4%) developed neutropenia (3 [2%] febrile neutropenia) after rituximab administration. Three patients (2%) developed posterior reversible leukoencephalopathy.

**Section Summary**

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

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

**Systemic Sclerosis (Scleroderma)**

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 1,000 mg IV weekly for 2 weeks. Immunosuppressive therapies included prednisone, methotrexate, azathioprine, MMF, and cyclophosphamide. Median follow-up was 7 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 9 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 vs 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 6 studies of rituximab (1 controlled trial [reviewed next], 3 cohort studies, 3 case reports; total N=36) were identified. No study reported improvements in HAQ-DI, and resolution of joint pain was reported in 1 patient. 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 1 study each.

Daoussis et al. (2010) assigned (by birth date) 14 patients with diffuse scleroderma to standard treatment plus 2 cycles of rituximab (375 mg/m2 weekly for 4 doses) 6 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 1-year 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).

Several case reports and case series described improvements in pulmonary function or decline in the rate of progression in patients with interstitial lung disease and improvements in skin symptoms with add-on rituximab (total N=25). All but 1 treatment-naive patient were refractory to standard immunosuppressive therapy. SAEs occurred in 7 patients (28%), including 2 sepsis deaths. Two reports described benefit with rituximab cycles administered at 6-month intervals.

Section Summary

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

Graft-Versus-Host Disease

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 7 cohort studies (total N=111) of rituximab in chronic GVHD. Three studies were prospective and 4 were retrospective. Poolled overall response rate was 66% (95% CI: 57 to 74). Indication-specific response rates were 13% to 100% for skin, 0% to 83% for oral mucosa, 0% to 66% for liver, and 0% to 38% for lung. Common AEs were infusion reactions or infectious complications.

In 2010, Kim et al. published a multicenter, Phase II cohort study of 37 patients with steroid-refractory chronic GVHD diagnosed according to National Institute of Health criteria. Most transplants used myeloablative conditioning regimens (78%) and unrelated donor cells. Patients received rituximab 375 mg/m² weekly for 4 weeks and then monthly for 4 months; 29 patients completed treatment (4 dropped out, 4 died), and 22 completed 8 additional months of follow-up (2 dropped out, 5 died). Thirty-two patients (86%) had any response (CR or PR) at any time during the study; median time to response was 29 days (range, 0-252). Twenty-one patients (57%) maintained response for 1 year, of whom 6 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 (eg, 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 and myelodysplastic syndromes. Systemic immunosuppressants were tapered per institutional standards. Thirty-two patients (49%) received all 4 rituximab infusions (median, 3); most common reasons for not completing the treatment course were development of GVHD and relapse. All patients had at least 2 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 4-year relapse (34%) and nonrelapse 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%; 1 of 2 lethal infections was considered possibly related to rituximab.

Arai et al. (2012) administered rituximab 375 mg/m2 on posttransplantation 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 4 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/µL) developed in 40% of patients, with febrile neutropenia and infection in 1 patient. Fifteen patients (43%) had severe grade 3 infections within 1 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 2 small cohort studies, 1 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 SAEs with rituximab, improved health outcomes in the prophylactic setting cannot be assumed.

Solid Organ Transplantation

Pretransplant Desensitization

Patients who are HLA-sensitized have broadly reactive alloantibodies, eg, 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 (ie, 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 PE (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 pretransplant desensitization with IVIG plus rituximab or IVIG plus placebo. Of 15 patients enrolled, 13 underwent transplantation. However, after 5 serious events were observed in 7 patients who were randomized to placebo (antibody-mediated rejection [ABMR] in 3 patients and graft loss in 2 patients), the trial was halted. No ABMR or graft loss occurred in 6 rituximab-treated patients. Mean (SD) serum creatinine levels at 6 and 12 months were 1.7 (0.5) mg/dL and 2.0 (0.6) mg/dL, respectively, in 2 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, 1 (17%) of 6 patients randomized to rituximab had undergone previous transplant compared with 5 (70%) of 7 patients randomized to placebo.

This same group reported 3 previous cohort studies of induction immunosuppression with rituximab plus IVIG in HLA-sensitized renal transplant recipients (total N≈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 3-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% to 20% of kidney transplants and can cause nephropathy, rejection, and graft dysfunction and failure. Barbosa et al (2014) compared 2 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 (ie, with anti-thymocyte globulin or alemtuzumab; 78%) than in the non-desensitized group (38%). At 2 years posttransplant, 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**

Antibody-mediated injury to allografts comprises ABMR, ABMR without complement deposition, antibody-mediated endarteritis, and accelerated arteriosclerosis of allografts.\textsuperscript{117} Induction immunosuppressive regimens initiated before, at the time of, or immediately after transplantation, mute T-cell responses to antigen presentation, reducing acute rejection.\textsuperscript{118} Induction regimens typically are combination high-dose immunosuppressive agents or anti-T-cell antibodies (eg, antithymocyte 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.\textsuperscript{119} Literature was searched through July 2013, and 7 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 5 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 4 studies showed increased graft survival at 1 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.\textsuperscript{120} 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 6 months after transplant, there was no statistical between-group differences in treatment failures (10 rituximab, 14 placebo; p=0.348), rejection episodes (8 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 3-year follow-up, 8 (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 1 patient each, and 6 cardiac arrests. Pretreatment 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 2 studies received deceased donor allografts. Graft failure occurred in 3 (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 1 week. At year 3, patient survival was 75% and 29% in the rituximab and control groups, respectively (p=0.009). Infections and rehospitalizations occurred in 4 (31%) and 8 (65%) of 13 rituximab-treated patients, respectively, and in 2 (10%) and 7 (35%) of 20 controls.

Zarkhin et al. (2008) reported on an open-label RCT of 20 consecutive pediatric patients (age range, 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 4 doses (n=10). All patients completed rituximab dosing without SAEs through 12 months of follow-up. Statistically significant improvements in creatinine clearance were seen in the rituximab group compared with the control group at 6 and 12 months after treatment (p for trend, 0.026).

ABMR after pancreatic transplantation is less common than cell-mediated rejection, but when it occurs, pancreatic islet cells appear to be particularly susceptible to injury. Use of rituximab has been described in 4 patients who underwent pancreas transplantation and developed ABMR (ie, graft dysfunction in the presence of anti-HLA antibodies with or without complement deposition on histopathological staining). In a series of 18 patients reported by Torrealba et al. (2008), 1 received rituximab plus IV corticosteroid, IVIG, and plasmapheresis for ABMR after simultaneous pancreas-kidney transplantation. This patient subsequently required chronic insulin therapy for blood glucose control. Three patients with type 1 diabetes mellitus (T1DM) who underwent simultaneous pancreas-kidney transplantation and developed ABMR received single doses of rituximab 375 mg/m2 in combination with T-cell-directed therapies (thymoglobulin and daclizumab, an anti-CD-25 monoclonal antibody or IVIG and plasmapheresis. Two patients in the first group remained insulin-independent for 36 months
and 12 months, and 1 patient in the second group remained insulin-independent for 10 months of follow-up.

**Pancreatic Islet Transplantation**

Autoimmune destruction of insulin-secreting islet beta-cells causes T1DM.\textsuperscript{128} Pancreatic islet transplantation is used in patients who have T1DM complicated by recurrent severe hypoglycemic episodes, and insulin independence is restored in 44\% of patients.\textsuperscript{129} However, graft function commonly declines over time, which is thought to be at least in part to allograft rejection. Immunosuppression management after islet transplantation is not standardized. Use of rituximab in a patient with evidence of ABMR has been described in a single case report.\textsuperscript{130}

A 51 year-old woman with a 26-year history of T1DM was insulin-independent 2 weeks after islet transplantation. Approximately 4 years later, glucose control deteriorated, and anti-HLA antibodies were detected. Two doses of IVIG plus rituximab 375 mg/m² were administered 2 weeks apart. Patient regained insulin-independence, which was maintained for 10 months of follow-up. An infectious complication occurred at the end of follow-up but was not described.\textsuperscript{130} This evidence is insufficient to establish (1) whether rituximab in combination with IVIG provides greater benefit than either treatment alone, and (2) whether rituximab improves net health outcomes, given its potentially SAEs.

**Section Summary**

Rituximab has been studied in the setting of solid organ (primarily kidney) transplantation for pretransplant desensitization, induction immunosuppressive therapy, and treatment of antibody-mediated rejection. Several cohort studies in sensitized individuals demonstrated good patient and graft survival with rituximab desensitization 3 years after transplant. An RCT comparing desensitization regimens with and without rituximab was terminated due to excess serious adverse events in the control arm, and 1 study reported no increase in polyomavirus BK-associated nephropathy at 2-year 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 ABMR comprised a meta-analysis of 5 very low-quality trials and 1 RCT. Although the meta-analysis indicated reduced ABMR and improved graft survival compared with controls, trial quality was very low. The RCT demonstrated increased mortality in the rituximab group at 3 years of follow-up. Rituximab has not been
shown to improve health outcomes when used for induction immunosuppression in kidney transplant recipients.

Small numbers of heart and kidney transplant recipients with ABMR have been treated with rituximab in comparative studies. Although observed improvements in outcomes suggest potential benefit with rituximab, data are retrospective or from small prospective studies. Comparative studies of rituximab for ABMR after pancreas transplantation were not identified. Dose-response studies and larger RCTs with longer follow-up and are needed to demonstrate improved health outcomes with rituximab treatment of ABMR.

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

**Ongoing and Unpublished Clinical Trials**

A search of ClinicalTrials.gov returned 41 randomized trials for 19 non-oncologic uses of rituximab that are currently recruiting participants. These are listed in Table 2. Additionally, a double-blind RCT of rituximab in patients with primary Sjögren syndrome is registered at the European Clinical Trials register (www.clinicaltrialsregister.eu; EudraCT Number, 2010-021430-64).

**Table 2. Randomized Trials of Rituximab for Non-oncologic Uses That Are Currently Recruiting Participants**

<table>
<thead>
<tr>
<th>Title</th>
<th>Phase</th>
<th>Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acquired hemophilia</td>
<td>3</td>
<td>164</td>
<td>Nov. 2018</td>
</tr>
<tr>
<td>Outcome of Acquired Hemophilia With Steroid Combined With Cyclophosphamide Versus Steroid Combined With Rituximab (CREHA Study) (NCT01808911)</td>
<td>3</td>
<td>164</td>
<td>Nov. 2018</td>
</tr>
<tr>
<td>Rituximab Vasculitis Maintenance Study NCT01697267 (NCT01697267)</td>
<td>3</td>
<td>190</td>
<td>Dec. 2016</td>
</tr>
<tr>
<td>Presolid organ transplant desensitization</td>
<td>1/2</td>
<td>75</td>
<td>Sep. 2018</td>
</tr>
<tr>
<td>Use of Immune Globulin (IVIG) Plus Rituximab</td>
<td>1/2</td>
<td>75</td>
<td>Sep. 2018</td>
</tr>
<tr>
<td>Title</td>
<td>Phase</td>
<td>Enrollment&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Completion Date</td>
</tr>
<tr>
<td>-----------------------------------------------------------------------</td>
<td>-------</td>
<td>------------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>for Desensitization in Highly HLA Sensitized Patients Awaiting Deceased Donor Kidney Transplantation (&lt;NCT01178216&gt;)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combined Apheresis for ABO-incompatible Transplantation - a Pilot Study (&lt;NCT02120482&gt;)</td>
<td>2</td>
<td>10</td>
<td>Sep. 2016</td>
</tr>
<tr>
<td>Postorgan transplant immunosuppression</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RituxiMab INDuction in Renal Transplantation (&lt;NCT01095172&gt;)</td>
<td>4</td>
<td>612</td>
<td>Oct. 2023</td>
</tr>
<tr>
<td>Rituximab to Prevent Recurrence of Proteinuria (&lt;NCT01164098&gt;)</td>
<td>2/3</td>
<td>40</td>
<td>Feb. 2016</td>
</tr>
<tr>
<td>Prevention of Cardiac Allograft Vasculopathy Using Rituximab (Rituxan) Therapy in Cardiac Transplantation (&lt;NCT01278745&gt;)</td>
<td>2</td>
<td>300</td>
<td>Aug. 2016</td>
</tr>
<tr>
<td>Long-term Function of Beta Cell Allografts in Non-uremic Type 1 Diabetic Patients (&lt;NCT00798785&gt;)</td>
<td>1/2</td>
<td>50</td>
<td>Dec. 2014</td>
</tr>
<tr>
<td>Acute cellular rejection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efficacy of Rituximab in Acute Cellular Rejection in Renal Transplant Patients (&lt;NCT01117662&gt;)</td>
<td>3</td>
<td>118</td>
<td>May. 2016</td>
</tr>
<tr>
<td>Chronic transplant rejection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study of Rituximab to Treat Chronic Renal Transplant Rejection (&lt;NCT00476164&gt;)</td>
<td>4</td>
<td>120</td>
<td>Jan. 2018</td>
</tr>
<tr>
<td>Idiopathic pulmonary fibrosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autoantibody Reduction Therapy in Patients With Idiopathic Pulmonary Fibrosis (&lt;NCT01969409&gt;)</td>
<td>2</td>
<td>58</td>
<td>Oct. 2018</td>
</tr>
<tr>
<td>A MultiCenter Study of Combined PEX, Rituximab, and Steroids in Acute Idiopathic Pulmonary Fibrosis Exacerbations (&lt;NCT01524068&gt;)</td>
<td>2</td>
<td>40</td>
<td>Jun. 2015</td>
</tr>
<tr>
<td>Graft-versus-host disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imatinib and Rituximab in Treating Cutaneous Sclerosis in Patients With Chronic Graft-Versus-Host Disease (&lt;NCT01309997&gt;)</td>
<td>2</td>
<td>74</td>
<td>Mar. 2016</td>
</tr>
<tr>
<td>Idiopathic membranous nephropathy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Title</td>
<td>Phase</td>
<td>Enrollment$^a$</td>
<td>Completion Date</td>
</tr>
<tr>
<td>----------------------------------------------------------------------</td>
<td>-------</td>
<td>----------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Membranous Nephropathy Trial Of Rituximab (NCT01180036)</td>
<td>2/3</td>
<td>126</td>
<td>Jun. 2016</td>
</tr>
<tr>
<td>Evaluate Rituximab Treatment for Idiopathic Membranous Nephropathy (NCT01508468)</td>
<td>3</td>
<td>80</td>
<td>Jan. 2015</td>
</tr>
<tr>
<td>Sequential Therapy With Tacrolimus and Rituximab in Primary Membranous Nephropathy (NCT01955187)</td>
<td>3</td>
<td>148</td>
<td>Jan. 2018</td>
</tr>
<tr>
<td><strong>IgA nephropathy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rituximab in Progressive IgA Nephropathy (NCT00498368)</td>
<td>4</td>
<td>54</td>
<td>Apr. 2014</td>
</tr>
<tr>
<td><strong>Immune thrombocytopenic purpura</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recombinant Human Thrombopoietin (rhTPO) Combining Rituximab Versus High-dose Dexamethasone for Initial Treatment of Primary Immune Thrombocytopenia (ITP) (NCT01734057)</td>
<td>3</td>
<td>240</td>
<td>Oct. 2013</td>
</tr>
<tr>
<td><strong>Lupus nephritis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RING - Rituximab for Lupus Nephritis With Remission as a Goal (NCT01673295)</td>
<td>3</td>
<td>194</td>
<td>Nov. 2016</td>
</tr>
<tr>
<td>Comparison of the Efficacy of Two Rituximab Treatment Regimens in Patients With Lupus Nephropathy (NCT01765842)</td>
<td>3</td>
<td>36</td>
<td>Dec. 2015</td>
</tr>
<tr>
<td>Trial of Rituximab and Mycophenolate Mofetil Without Oral Steroids for Lupus Nephritis</td>
<td>3</td>
<td>252</td>
<td>Aug. 2017</td>
</tr>
<tr>
<td>Title</td>
<td>Phase</td>
<td>Enrollment</td>
<td>Completion Date</td>
</tr>
<tr>
<td>----------------------------------------------------------------------</td>
<td>-------</td>
<td>------------</td>
<td>-----------------</td>
</tr>
<tr>
<td><strong>Multiple sclerosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Double Blind Combination of Rituximab by Intravenous and Intrathecal Injection Versus Placebo in Patients With Low-Inflammatory Secondary Progressive Multiple Sclerosis (RIVITaLiSe) (NCT01212094)</td>
<td>1/2</td>
<td>80</td>
<td>Sep. 2016</td>
</tr>
<tr>
<td><strong>Myasthenia gravis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase II Trial of Rituximab In Myasthenia Gravis (NCT02110706)</td>
<td>2</td>
<td>50</td>
<td>Dec. 2017</td>
</tr>
<tr>
<td><strong>Pancreatic Islet Transplantation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long-term Function of Beta Cell Allografts in Non-uremic Type 1 Diabetic Patients (NCT00798785)</td>
<td>1/2</td>
<td>50</td>
<td>Dec. 2014</td>
</tr>
<tr>
<td><strong>Pemphigus disease</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comparative Study of Rituximab Versus Combination of Rituximab and Intravenous Cyclophosphamide in Severe Pemphigus (NCT01974518)</td>
<td>3</td>
<td>20</td>
<td>Jun. 2015</td>
</tr>
<tr>
<td>Comparison Between Rituximab Treatment and General Corticotherapy Treatment in Patients With Pemphigus (NCT00784589)</td>
<td>3</td>
<td>90</td>
<td>Aug. 2016</td>
</tr>
<tr>
<td><strong>Pediatric nephrotic syndrome</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rituximab Trial for Pediatric Nephrotic Syndrome (NCT01716442)</td>
<td>2/3</td>
<td>88</td>
<td>Nov. 2013</td>
</tr>
<tr>
<td><strong>Systemic sclerosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rituximab in Systemic Sclerosis (NCT01748084)</td>
<td>2/3</td>
<td>90</td>
<td>Jun. 2015</td>
</tr>
<tr>
<td>Rituximab for Treatment of Systemic Sclerosis-Associated Pulmonary Arterial Hypertension (SSc-PAH) (NCT01086540)</td>
<td>2</td>
<td>80</td>
<td>Jan. 2015</td>
</tr>
<tr>
<td>Rituximab Versus Cyclophosphamide in Connective Tissue Disease-ILD (NCT01862926)</td>
<td>2/3</td>
<td>116</td>
<td>Jun. 2016</td>
</tr>
<tr>
<td><strong>Rheumatoid arthritis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Title</td>
<td>Phase</td>
<td>Enrollment&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Completion Date</td>
</tr>
<tr>
<td>-------</td>
<td>-------</td>
<td>------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>A Randomized, Multi-Center Biomarker Trial to Predict Therapeutic Responses of Patients With Rheumatoid Arthritis to a Specific Biologic Mode of Action (NCT01638715)</td>
<td>4</td>
<td>200</td>
<td>Jun. 2015</td>
</tr>
<tr>
<td>PK Similarity Prospective Phase 3 Study in Patients With Rheumatoid Arthritis (NCT02149121)</td>
<td>3</td>
<td>300</td>
<td>Jul. 2017</td>
</tr>
<tr>
<td>Study of Safety and Efficacy of BCD-020 Comparing to MabThera in Patients With Rheumatoid Arthritis (NCT01759030)</td>
<td>3</td>
<td>308</td>
<td>Jul. 2015</td>
</tr>
<tr>
<td>SWITCH Clinical Trial for Patients With Rheumatoid Arthritis Who Have Failed an Initial TNF-blocking Drug (NCT01295151)</td>
<td>4</td>
<td>477</td>
<td>Dec. 2015</td>
</tr>
<tr>
<td>Optimal Management of Rheumatoid Arthritis Patients Requiring Biologic Therapy (NCT01021735)</td>
<td>4</td>
<td>302</td>
<td>Jun. 2014</td>
</tr>
<tr>
<td><strong>Warm autoimmune hemolytic anemia</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ANCA: antineutrophil cytoplasmic antibody.
<sup>a</sup> Expected.
<sup>b</sup> Estimated.

**Clinical Input Received From Physician Specialty Societies and Academic Medical Centers**

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

**2014 Input**

In response to requests, input was received from 9 physician specialty societies (16 reviewers) and 1 academic medical center while this policy was under review in 2014. Overall, input
supported the policy statements as currently written. Exceptions included Churg-Strauss syndrome (most reviewers considered rituximab medically necessary and supported first-line use [induction therapy] for severe disease) and acquired thrombotic thrombocytopenic purpura (reviewers were split). Other suggested indications were chronic inflammatory demyelinating polyneuropathy, IgM-related demyelinating neuropathies, myasthenia gravis, Lambert-Eaton myasthenic syndrome, ABO incompatible organ/tissue grafts, and post-solid organ transplant membranous nephropathy.

**Summary of Evidence**

**Food and Drug Administration–Approved Uses**

**Rheumatoid Arthritis**

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

**Autoimmune Hemolytic Anemia**

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

Rituximab is being studied as a splenectomy-delaying or -avoiding approach in patients with idiopathic thrombocytopenic purpura (ITP). Two systematic reviews of primarily observational studies (1 in children [median age, 8 years], 1 in adults) and 2 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 1 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. AE 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**

Studies of rituximab in 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 (PE) treatments needed to achieve remission. For patients with relapsed or refractory TTP, observational studies (case reports and case series) reported remission in 98% of rituximab-treated patients with a median follow-up of 10 months. This evidence suggests that, despite a small (3%) risk of serious adverse events (SAEs) with rituximab, some patients treated with PE who have relapsed or refractory disease may benefit from the addition of rituximab. Because progressive disease is potentially life-threatening and because relapsed and refractory patients have few alternative treatment options, rituximab may be considered medically necessary in this setting. Approximately half of clinical reviewers who provided input when this policy was under review in 2014 supported the use of rituximab in TTP. A single case series of rituximab prophylaxis for recurrent disease provides insufficient evidence for use of rituximab in this setting.

**Churg-Strauss Syndrome**

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

**Factor Inhibitors in Hemophilia**

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

**Hepatitis C Virus–associated Cryoglobulinemic Vasculitis**

Recent reviews summarized the literature for rituximab to treat hepatitis C virus (HCV)–associated cryoglobulinemic vasculitis. Across 2 RCTS and many observational studies (total N=377), median overall response was approximately 80%. However, these studies were done before the advent of several new HCV antiviral drugs and pegylated interferon–free drug regimens. More effective antiviral treatments should improve outcomes, eg, virologic and immunologic responses and cure rate of both HCV and associated vasculitis. However, for

---

Page | 53 of 74
patients with antiviral-resistant active disease or with severe or life-threatening cryoglobulinemic vasculitis, rituximab in combination with current treatments may improve health outcomes. Viral load and liver function tests should be monitored during rituximab treatment.

**Mixed Connective Tissue Disease**

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

**Multicentric Castleman Disease**

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

**Multiple Sclerosis**

One RCT in patients with relapsing-remitting multiple sclerosis showed improvements in magnetic resonance imaging and clinical outcomes at 24 weeks of follow-up. However, methodologic limitations restrict the conclusions that can be based on these data. One well-designed RCT in patients with primary progressive multiple sclerosis 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 (eg, ß-interferon and glatiramer acetate), efficacy of rituximab appeared comparable with that of azathioprine and mycophenolate mofetil (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 1 retrospective comparative study in ocular cicatricial pemphigoid. Patients were refractory to previous treatments, but most (75%-100%) responded to rituximab. Infections, including serious and fatal infections, were reported in 4% to 19% of patients, but AE reporting may have been incomplete. Only 3 of 8 pemphigoid diseases were examined in the literature: epidermolysis bullosa acquisita, bullous pemphigoid, and mucous membrane pemphigoid. Although the body of evidence is small, disease progression can lead to serious outcomes (eg, blindness) or death, reported response rates were high, and treatment options in refractory patients are limited. For these reasons, rituximab may be considered medically necessary for treatment of the pemphigoid and pemphigus diseases reviewed in the literature in treatment-refractory patients.

Primary Sjögren Syndrome

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

**Systemic Lupus Erythematosus**

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

**Lupus Nephritis**

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

**Systemic Sclerosis (Scleroderma)**

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

**Graft-Versus-Host Disease**

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

Evidence for rituximab prophylaxis for GVHD comprises 2 small cohort studies, 1 of which included a contemporaneous control group. Although results suggested that rituximab may reduce the incidence of GVHD, replication in larger, controlled trials is needed. Due to the risk of severe AEs with rituximab, improved health outcomes in the prophylactic setting cannot be assumed.

**Pretransplant Desensitization**

Rituximab has been studied in the setting of solid organ (primarily kidney) transplantation for pretransplant desensitization, induction immunosuppressive therapy, and treatment of antibody-mediated rejection. Several cohort studies in sensitized individuals demonstrated good patient and graft survival with rituximab desensitization 3 years after transplant. An RCT comparing desensitization regimens with and without rituximab was terminated due to excess SAEs in the control arm, and 1 study reported no increase in polyomavirus BK-associated nephropathy at 2-year follow-up. This evidence suggests that health outcomes are improved with rituximab desensitization regimens in sensitized renal transplant candidates.

**Antibody-Mediated Rejection**

Evidence for rituximab induction to prevent acute antibody-mediated rejection (ABMR) comprised a meta-analysis of 5 very low-quality trials and 1 RCT. Although the meta-analysis indicated reduced ABMR and improved graft survival compared with controls, trial quality was very low. The RCT demonstrated increased mortality in the rituximab group at 3-year follow-up. Rituximab has not been shown to improve health outcomes when used for induction immunosuppression in kidney transplant recipients.
Small numbers of heart and kidney transplant recipients with ABMR have been treated with rituximab in comparative studies. Although observed improvements in outcomes suggest potential benefit with rituximab, data are retrospective or from small prospective studies. Dose-response studies and larger RCTs with longer follow-up and are needed to demonstrate improved health outcomes with rituximab treatment of ABMR.

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

Practice Guidelines and Position Statements

Rheumatoid Arthritis

American College of Rheumatology

The American College of Rheumatology (ACR) updated its evidence-based consensus guidelines in 2012 and made the following recommendations:

- If a patient has moderate (eg, Clinical Disease Activity Index [CDAI] >10-22 or Disease Activity Score in 28 joints [DAS-28] ≥3.2 to ≤5.1) or high (eg, CDAI >22 or DAS-28 >5.1) disease activity after 3 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 3 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 6 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 5 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**

The European League Against Rheumatism's (EULAR) 2013 recommendations for the management of RA with synthetic and biological 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-naive patients.

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

Kidney Diseases: Improving Global Outcomes

In 2012, Kidney Diseases: Improving Global Outcomes (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**

In 2011, American Society of Hematology 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 1 line of therapy, such as corticosteroid, IVIG, or splenectomy, and are at risk of bleeding.

**Thrombotic Thrombocytopenic Purpura**

**British Committee for Standards in Haematology**

The British Committee for Standards in Haematology (BCSH) 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 4 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, National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America**

In 2013, the Centers for Disease Control and Prevention (CDC), National Institutes of Health (NIH), and the HIV Medicine Association (HIVMA) of the Infectious Diseases Society of America (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 [1 or more nonrandomized trials or observational studies with long-term clinical outcomes]).

**CDC, NIH, HIVMA/IDSA, Pediatric Infectious Diseases Society, and American Academy of Pediatrics**

In 2013, CDC, NIH, HIVMA/IDSA, Pediatric Infectious Diseases Society, and the American Academy of Pediatrics 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**

The American Academy of Neurology’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

In April 2014, National Institute for Health and Care Excellence issued draft guidance for the management of MS in primary and secondary care.\textsuperscript{139} It does not include rituximab.

National Multiple Sclerosis Society

The National Multiple Sclerosis Society does not include rituximab among its listed treatments for MS.\textsuperscript{340}

Neuromyelitis Optica

Neuromyelitis Optica Study Group

In 2014, Neuromyelitis Optica Study Group published evidence-based consensus recommendations on the diagnosis and treatment of neuromyelitis optica.\textsuperscript{65} 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

In 2013, UK Haemophilia Centre Doctors Organization updated its evidence-based consensus guideline for the diagnosis and treatment of factor VIII and factor IX inhibitors in congenital hemophilia.\textsuperscript{33} For patients undergoing ITI, rituximab is suggested as 1 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 6 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–Associated Cryoglobulinemic Vasculitis

*Kidney Diseases: Improving Global Outcomes*

In 2012, KDIGO published evidence-based consensus guidelines for glomerulonephritis. Rituximab in combination with IV methylprednisolone and antiviral therapy is suggested as 1 of several treatment options (along with plasmapheresis or cyclophosphamide, also in combination with IV methylprednisolone and antiviral therapy) for patients with hepatitis C virus 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*

In 2012, the British Association of Dermatologists 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*

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 6 months of 1 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 and European Renal Association–European Dialysis and Transplant Association**

In 2012, EULAR and the European Renal Association–European Dialysis and Transplant Association published joint evidence-based consensus recommendations for the management of pediatric and adult lupus nephritis. For refractory disease, ie, 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 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).

**Kidney Diseases: Improving Global Outcomes**

In 2012, KDIGO published evidence-based consensus guidelines for glomerulonephritis. Rituximab is suggested as 1 of several treatment options (along with IVIG and calcineurin inhibitors) for patients with lupus nephritis who have failed more than 1 first-line regimen (level 2 suggestion based on level D [very low quality] evidence).

**Graft-Versus-Host Disease**

**British Committee for Standards in Haematology**

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), BSCH does not recommend rituximab for acute GVHD.

- For chronic GVHD, BCSH makes 2 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.\textsuperscript{107} 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

In 2012, the International Society of Heart and Lung Transplantation published evidence-based consensus guidelines for the care of heart transplant recipients.\textsuperscript{145} 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)

Kidney Diseases: Improving Global Outcomes

In 2009, KDIGO published evidence-based consensus guidelines for the care of kidney transplant recipients.\textsuperscript{118} 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.
U.S. Preventive Services Task Force Recommendations

Rituximab for the treatment of various conditions is not a preventive service.

Medicare National Coverage

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

References


**History**

<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>01/13/15</td>
<td>New policy, created with literature review through May 5, 2014. Add to Pharmacy section. Policy outlines the non-oncologic labeled and off-label indications for which Rituximab is considered medically necessary.</td>
</tr>
<tr>
<td>Date</td>
<td>Comments</td>
</tr>
<tr>
<td>------------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>07/15/15</td>
<td>Minor edit. Removed link to policy 5.01.550.</td>
</tr>
<tr>
<td>07/01/16</td>
<td>Annual review, approved June 14, 2016. Medical necessity review criteria for site of service IV therapy added. Policy reformatted and reorganized.</td>
</tr>
<tr>
<td>08/01/16</td>
<td>Operational clarification. Clarified that medical necessity reviews for cancer diagnoses use policy 2.03.502.</td>
</tr>
<tr>
<td>11/01/16</td>
<td>Interim review, approved October 11, 2016. Clarified age criteria language indicating that site of service review is applicable to only those age 13 and older; drug criteria review applies to all ages.</td>
</tr>
<tr>
<td>04/21/17</td>
<td>Minor edit. Introduction section revised for clarity.</td>
</tr>
<tr>
<td>07/01/17</td>
<td>Formatting edit; added hyperlink menu for Medical Necessity Criteria sections.</td>
</tr>
</tbody>
</table>

**Disclaimer:** This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2017 Premera All Rights Reserved.

**Scope:** Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.
Discrimination is Against the Law

Premera Blue Cross complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability, or sex. Premera does not exclude people or treat them differently because of race, color, national origin, age, disability or sex.

Premera:
- Provides free aids and services to people with disabilities to communicate effectively with us, such as:
  - Qualified sign language interpreters
  - Written information in other formats (large print, audio, accessible electronic formats, other formats)
- Provides free language services to people whose primary language is not English, such as:
  - Qualified interpreters
  - Information written in other languages

If you need these services, contact the Civil Rights Coordinator.

If you believe that Premera has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability, or sex, you can file a grievance with:
Civil Rights Coordinator - Complaints and Appeals
PO Box 91102, Seattle, WA 98111
Toll free 855-332-4535, Fax 425-918-5592, TTY 800-842-5357
Email AppealsDepartmentInquiries@Premera.com

You can file a grievance in person or by mail, fax, or email. If you need help filing a grievance, the Civil Rights Coordinator is available to help you.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at:
https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at:
U.S. Department of Health and Human Services
200 Independence Avenue SW, Room 509F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)
Complaint forms are available at

Getting Help in Other Languages

This Notice has Important Information. This notice may have important information about your application or coverage through Premera Blue Cross. There may be key dates in this notice. You may need to take action by certain deadlines to keep your health coverage or help with costs. You have the right to get this information and help in your language at no cost. Call 800-722-1471 (TTY: 800-842-5357).

Oromoo (Cushite):

Français (French):

Deutsche (German):

Hmoob (Hmong):

Iloko (Ilocano):
Daytoy a Pakdaar ket naglao iti Napateg nga Impormasion. Daytoy a pakdaar mabalin nga adda ket naglao iti napateg nga impormasion maianggepp iti aplikayonyo weny coverage babaen iti Premera Blue Cross. Daytoy ket mabalin dagiti importante a pelsa iti daytoy a pakdaar. Mabalin nga adda rambeg nga aramidenyo nga addang sakbay dagiti partikular a naituding nga aldaw tampos kayayoon nga impormasion iti bagayyanon. Damaa nqorun anir damma kaj nyong taulim nga sakyoon nga adadda nga adadda nga adadda nga adadda. Daytro daytoy nga impormasion ken taulim iti bukodyo a pagasasao nga awan ti bayadanyon. Tumawag iti numero nga 800-722-1471 (TTY: 800-842-5357).

Italiano (Italian):

中文 (Chinese):
本通知有重要的訊息。本通知可能有關於您透過 Premera Blue Cross 提交的申請或保險的重要訊息。本通知可能有重要日期。您可能需要在截止日期之前採取行動，以保留您的健康保險或費用補貼。您有權利免費以您的母語得到本訊息和幫助。請撥電話 800-722-1471 (TTY: 800-842-5357).
Premera Blue Cross

Những thông tin quan trọng của bạn có thể sẽ được ghi nhận trong Bảng thông tin của bạn. Đối với người có Bảo hiểm của Premera Blue Cross, thông tin này sẽ có thể bao gồm:

- Thông tin về Bảo hiểm của bạn
- Thông tin về quyền lợi và chi phí của bạn
- Thông tin về việc sử dụng dịch vụ y tế của bạn

Thông tin này sẽ được cung cấp cho bạn thông qua một số phương tiện bao gồm:

- Điện thoại: 800-722-1471 (TTY: 800-842-5357)
- Website: www.premerabluecross.com

Thông tin này được cung cấp bởi Premera Blue Cross. Nếu bạn muốn biết thêm thông tin, hãy liên hệ với chúng tôi.

Giới thiệu với các dịch vụ và hỗ trợ của Premera Blue Cross:

1. Liên hệ với Premera Blue Cross:
   - Đừng ngần ngại liên hệ với Premera Blue Cross nếu bạn có bất kỳ câu hỏi nào.
   - Bạn có thể liên hệ với chúng tôi qua điện thoại 800-722-1471 (TTY: 800-842-5357).

2. Tham gia vào các chương trình y tế:
   - Bạn có thể tham gia vào các chương trình y tế của Premera Blue Cross như chương trình chăm sóc sức khỏe và chương trình chăm sóc sức khỏe ban đêm.
   - Bạn có thể liên hệ với chúng tôi để biết thêm thông tin chi tiết.

3. Hỗ trợ y tế:
   - Nếu bạn đang cần sự hỗ trợ y tế, bạn có thể liên hệ với Premera Blue Cross.
   - Bạn có thể liên hệ với chúng tôi qua điện thoại 800-722-1471 (TTY: 800-842-5357).

Thông tin này được cung cấp bởi Premera Blue Cross. Nếu bạn muốn biết thêm thông tin, hãy liên hệ với chúng tôi.

Giới thiệu với các dịch vụ và hỗ trợ của Premera Blue Cross:

1. Liên hệ với Premera Blue Cross:
   - Đừng ngần ngại liên hệ với Premera Blue Cross nếu bạn có bất kỳ câu hỏi nào.
   - Bạn có thể liên hệ với chúng tôi qua điện thoại 800-722-1471 (TTY: 800-842-5357).

2. Tham gia vào các chương trình y tế:
   - Bạn có thể tham gia vào các chương trình y tế của Premera Blue Cross như chương trình chăm sóc sức khỏe và chương trình chăm sóc sức khỏe ban đêm.
   - Bạn có thể liên hệ với chúng tôi để biết thêm thông tin chi tiết.

3. Hỗ trợ y tế:
   - Nếu bạn đang cần sự hỗ trợ y tế, bạn có thể liên hệ với Premera Blue Cross.
   - Bạn có thể liên hệ với chúng tôi qua điện thoại 800-722-1471 (TTY: 800-842-5357).

Thông tin này được cung cấp bởi Premera Blue Cross. Nếu bạn muốn biết thêm thông tin, hãy liên hệ với chúng tôi.

Giới thiệu với các dịch vụ và hỗ trợ của Premera Blue Cross:

1. Liên hệ với Premera Blue Cross:
   - Đừng ngần ngại liên hệ với Premera Blue Cross nếu bạn có bất kỳ câu hỏi nào.
   - Bạn có thể liên hệ với chúng tôi qua điện thoại 800-722-1471 (TTY: 800-842-5357).

2. Tham gia vào các chương trình y tế:
   - Bạn có thể tham gia vào các chương trình y tế của Premera Blue Cross như chương trình chăm sóc sức khỏe và chương trình chăm sóc sức khỏe ban đêm.
   - Bạn có thể liên hệ với chúng tôi để biết thêm thông tin chi tiết.

3. Hỗ trợ y tế:
   - Nếu bạn đang cần sự hỗ trợ y tế, bạn có thể liên hệ với Premera Blue Cross.
   - Bạn có thể liên hệ với chúng tôi qua điện thoại 800-722-1471 (TTY: 800-842-5357).

Thông tin này được cung cấp bởi Premera Blue Cross. Nếu bạn muốn biết thêm thông tin, hãy liên hệ với chúng tôi.

Giới thiệu với các dịch vụ và hỗ trợ của Premera Blue Cross:

1. Liên hệ với Premera Blue Cross:
   - Đừng ngần ngại liên hệ với Premera Blue Cross nếu bạn có bất kỳ câu hỏi nào.
   - Bạn có thể liên hệ với chúng tôi qua điện thoại 800-722-1471 (TTY: 800-842-5357).

2. Tham gia vào các chương trình y tế:
   - Bạn có thể tham gia vào các chương trình y tế của Premera Blue Cross như chương trình chăm sóc sức khỏe và chương trình chăm sóc sức khỏe ban đêm.
   - Bạn có thể liên hệ với chúng tôi để biết thêm thông tin chi tiết.

3. Hỗ trợ y tế:
   - Nếu bạn đang cần sự hỗ trợ y tế, bạn có thể liên hệ với Premera Blue Cross.
   - Bạn có thể liên hệ với chúng tôi qua điện thoại 800-722-1471 (TTY: 800-842-5357).

Thông tin này được cung cấp bởi Premera Blue Cross. Nếu bạn muốn biết thêm thông tin, hãy liên hệ với chúng tôi.