

PHARMACY / MEDICAL POLICY – 5.01.556

Rituximab: Non-oncologic and Miscellaneous Uses

BCBSA Ref. Policy: 5.01.24

Effective Date: **July 1, 2025***
Last Revised: Feb. 11, 2025
Replaces: Extracted from
5.01.550

RELATED MEDICAL POLICIES:
2.03.502 Monoclonal Antibodies for the Treatment of Lymphoma
5.01.550 Pharmacotherapy of Arthropathies
11.01.523 Site of Service: Infusion Drugs and Biologic Agents

*This policy has been revised.
[Click here to view the current policy.](#)


The Site of Service Medical Necessity criteria within this policy DOES NOT apply to Alaska fully-insured members; refer to the infusion drug Medical Necessity criteria only.

Site of Service *and* the infusion drug Medical Necessity criteria apply to all other plan members.

Please contact Customer Service for more information.

Select a hyperlink below to be directed to that section.

[POLICY CRITERIA](#) | [DOCUMENTATION REQUIREMENTS](#) | [CODING](#)
[RELATED INFORMATION](#) | [EVIDENCE REVIEW](#) | [REFERENCES](#) | [HISTORY](#)

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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 Rituxan (rituximab) and the biosimilars Riabni (rituximab-arrx), Ruxience (rituximab-pvvr) and Truxima (rituximab-abbs) 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

Site of Service Medical Necessity criteria does NOT apply to Alaska fully-insured members; refer to the infusion drug Medical Necessity criteria only. Please contact Customer Service for more information.

Note: This policy does not apply if the member has a lymphoid cancer diagnosis such as lymphoma, leukemia, multiple myeloma, or Waldenstrom's macroglobulinemia (for these diagnoses see policy [2.03.502 Monoclonal Antibodies for the Treatment of Lymphoma](#)).

We will review specific intravenous (IV) and injectable drugs for medical necessity for all ages.

For those aged 13 years or 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:

- **First-line products:**
 - Ruxience (rituximab-pvvr)
 - Truxima (rituximab-abbs)
- **Second-line products:**
 - Riabni (rituximab-arrx)
 - Rituxan (rituximab)



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

[Autoimmune hemolytic anemias \(AIHA\)](#)

[Chronic Graft-Versus-Host Disease](#)

[Cryoglobulinemic Vasculitis Associated with Hepatitis-C Virus \(HCV\)](#)

[Desensitization of Human Leukocyte Antigen \(HLA\)](#)

[Eosinophilic Granulomatosis with polyangiitis \(Churg-Strauss syndrome\)](#)

[Hemophilia](#)

[Idiopathic Membranous Nephropathy](#)

[Idiopathic Thrombocytopenic Purpura](#)

[Lupus Nephritis](#)

[Microscopic Polyangiitis](#)

[Multicentric Castleman Disease](#)

[Neuromyelitis Optica Spectrum Disorders \(NMOSD\)](#)

[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](#)

Site of Service Administration	Medical Necessity
<p>Medically necessary sites of service</p> <ul style="list-style-type: none"> Physician's office Infusion center Home infusion 	<p>IV infusion therapy of various medical or biologic agents will be covered in the most appropriate, safe and cost effective site:</p> <ul style="list-style-type: none"> These are the preferred medically necessary sites of service for specified drugs.
<p>Hospital-based outpatient setting</p> <ul style="list-style-type: none"> Outpatient hospital IV infusion department 	<p>IV infusion therapy of various medical or biologic agents will be covered in the most appropriate, safe and cost-effective site.</p>



Site of Service Administration	Medical Necessity
<ul style="list-style-type: none"> Hospital-based outpatient clinical level of care 	<p>This site is considered medically necessary for the first 90 days for the following:</p> <ul style="list-style-type: none"> The initial course of infusion of a pharmacologic or biologic agent <p>OR</p> <ul style="list-style-type: none"> Re-initiation of an agent after 6 months or longer following discontinuation of therapy* <p>Note: *This does not include when standard dosing between infusions is 6 months or longer</p> <p>This site is considered medically necessary when there is no outpatient infusion center within 50 miles of the patient's home and there is no contracted home infusion agency that will travel to their home, or a hospital is the only place that offers infusions of this drug.</p> <p>This site is considered medically necessary only when the individual has a clinical condition which puts him or her at increased risk of complications for infusions, including any ONE of the following:</p> <ul style="list-style-type: none"> Known cardiac condition (e.g., symptomatic cardiac arrhythmia) or pulmonary condition (e.g., significant respiratory disease, serious obstructive airway disease, %FVC \leq 40%) that may increase the risk of an adverse reaction Unstable renal function which decreases the ability to respond to fluids Difficult or unstable vascular access Acute mental status changes or cognitive conditions that impact the safety of infusion therapy A known history of severe adverse drug reactions and/or anaphylaxis to prior treatment with a related or similar drug



Site of Service Administration	Medical Necessity
	<p>This site is considered medically necessary when the individual has cytokine release syndrome (CRS) and all the following are met:</p> <ul style="list-style-type: none"> • CRS is grade 3 or 4 as evidenced by ALL the following: <ul style="list-style-type: none"> ○ Temperature $\geq 38^{\circ}\text{C}$ ○ Hypotension that requires one or more vasopressors ○ Hypoxia that requires oxygen through a high-flow nasal cannula, face mask, non-rebreather mask, or Venturi mask OR positive pressure (continuous positive airway pressure [CPAP], bilevel positive airway pressure [BiPAP], intubation, or mechanical ventilation) <p>AND</p> <ul style="list-style-type: none"> • The individual will be admitted into an inpatient setting as soon as possible
<p>Hospital-based outpatient setting</p> <ul style="list-style-type: none"> • Outpatient hospital IV infusion department • Hospital-based outpatient clinical level of care 	<p>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.</p>

Condition	Medical Necessity
<p>Ruxience and Truxima are subject to review for site of service administration.</p>	
<p>Arthropathies</p>	
<p>Rheumatoid arthritis (RA)</p> <ul style="list-style-type: none"> • See also: Related Policy 5.01.550 Pharmacotherapy of Arthropathies • Related Policy 5.01.647 Medical Necessity Criteria for Custom Incentive and Open Formularies 	<p>Ruxience (rituximab-pvvr) or Truxima (rituximab-abbs) may be considered medically necessary when:</p> <ul style="list-style-type: none"> • Treating moderately to severely active rheumatoid arthritis (e.g., ≥ 8 swollen and ≥ 8 tender joints) <p>AND</p> <ul style="list-style-type: none"> • Is administered in combination with methotrexate <p>AND</p> <ul style="list-style-type: none"> • Is used as a second-line therapy when either: <ul style="list-style-type: none"> ○ The individual has tried and failed any one of the first line therapies listed below:



Condition	Medical Necessity
Ruxience and Truxima are subject to review for site of service administration.	
	<ul style="list-style-type: none"> ▪ A preferred adalimumab product*: Cyltezo (adalimumab-adbm), Simlandi (adalimumab-ryvk), adalimumab-adaz (Hyrimoz unbranded), adalimumab-adbm (Cyltezo unbranded), or adalimumab-ryvk (Simlandi unbranded) ▪ Enbrel (etanercept) ▪ Remicade (infliximab) ▪ Actemra (tocilizumab) ▪ Xeljanz (tofacitinib) / Xeljanz XR (tofacitinib extended release) ▪ Rinvoq (upadacitinib) <p>OR</p> <ul style="list-style-type: none"> ○ The individual has had an inadequate response to methotrexate or other conventional synthetic disease-modifying anti-rheumatic drug (DMARD) <p>AND</p> <ul style="list-style-type: none"> ○ Is not a suitable candidate for treatment with TNF inhibitors (e.g., due to a recent [i.e., within 5 years] history of lymphoma or other malignancy; latent tuberculosis, and contraindication to chemoprophylaxis; or previous demyelinating disease <p>*Note: This list of preferred adalimumab products does not apply to one Open formulary (Formulary ID: 6062; Rx Plan F1) and one Incentive formulary (Formulary ID: 6064; Rx Plan G3). More details can be found in policy 5.01.647 Medical Necessity Criteria for Custom Incentive and Open Formularies. Please check the member Plan booklet or member ID card to determine whether this list of preferred adalimumab products applies.</p>
Miscellaneous Autoimmune Diseases	
<p>Antineutrophil cytoplasmic antibody – associated (ANCA) vasculitides:</p> <ul style="list-style-type: none"> • Wegener’s granulomatosis (granulomatosis with polyangiitis) 	<p>Ruxience (rituximab-pvvr) or Truxima (rituximab-abbs) may be considered medically necessary for the treatment of granulomatosis with polyangitis and microscopic polyangitis when:</p> <ul style="list-style-type: none"> • Initial therapy with azathioprine, methotrexate and/or mycophenolate has been tried and failed or is contraindicated.



Condition	Medical Necessity
Ruxience and Truxima are subject to review for site of service administration.	
<ul style="list-style-type: none"> • Microscopic polyangiitis 	<p>AND</p> <ul style="list-style-type: none"> • Medication is used in combination with glucocorticoids.
<p>Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)</p>	<p>Ruxience (rituximab-pvvr) or Truxima (rituximab-abbs) may be considered medically necessary for the treatment of eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome) when:</p> <ul style="list-style-type: none"> • Used as first-line treatment in combination with glucocorticoids for individuals with severe (organ-threatening) disease <p>OR</p> <ul style="list-style-type: none"> • Medication is used as add-on therapy for treatment-refractory disease
<p>Cryoglobulinemic vasculitis associated with hepatitis-C virus (HCV)</p>	<p>Ruxience (rituximab-pvvr) or Truxima (rituximab-abbs) may be considered medically necessary for the treatment of cryoglobulinemic vasculitis associated with hepatitis-C virus when:</p> <ul style="list-style-type: none"> • Used as add-on therapy for individuals who have: <ul style="list-style-type: none"> ○ Active disease resistant to anti-viral drugs <p>OR</p> <ul style="list-style-type: none"> ○ Severe or life-threatening cryoglobulinemic vasculitis
<p>Idiopathic membranous nephropathy</p>	<p>Ruxience (rituximab-pvvr) or Truxima (rituximab-abbs) may be considered medically necessary for the treatment of idiopathic membranous nephropathy when:</p> <ul style="list-style-type: none"> • The individuals have failed prior treatment with other immunosuppressive regimens such as cyclophosphamide or chlorambucil plus glucocorticoids, or cyclosporine, or tacrolimus
<p>Lupus nephritis</p>	<p>Ruxience (rituximab-pvvr) or Truxima (rituximab-abbs) may be considered medically necessary for the treatment of lupus nephritis when:</p> <ul style="list-style-type: none"> • Used as add-on therapy in individuals who are refractory to at least two standard first-line treatment regimens, and initial treatment has been with any two of the following: <ul style="list-style-type: none"> ○ Cyclophosphamide, azathioprine, or other immunosuppressant ○ Glucocorticoid (in addition to the above)



Condition	Medical Necessity
Ruxience and Truxima are subject to review for site of service administration.	
Neuromyelitis optica spectrum disorders (NMOSD)	<p>Ruxience (rituximab-pvvr) or Truxima (rituximab-abbs) may be considered medically necessary for the treatment of neuromyelitis optica spectrum disorders (NMOSD) when the following are met:</p> <ul style="list-style-type: none"> • The individual has a documented diagnosis of NMOSD confirmed by: <ul style="list-style-type: none"> ○ At least one of the following core clinical characteristics: <ul style="list-style-type: none"> ▪ Optic neuritis ▪ Acute myelitis ▪ Area postrema syndrome: Episode of otherwise unexplained hiccups or nausea and vomiting ▪ Acute brainstem syndrome ▪ Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions ▪ Symptomatic cerebral syndrome with NMOSD-typical brain lesions <p>AND</p> <ul style="list-style-type: none"> ○ Exclusion of alternative diagnoses (e.g., multiple sclerosis)
Primary Sjögren syndrome	<p>Ruxience (rituximab-pvvr) or Truxima (rituximab-abbs) may be considered medically necessary for the treatment of primary Sjögren syndrome when:</p> <ul style="list-style-type: none"> • Used for individuals refractory to ALL of the following: <ul style="list-style-type: none"> ○ Glucocorticoids ○ Other immunosuppressive agents (e.g., hydroxychloroquine or methotrexate) ○ One of the following drugs: <ul style="list-style-type: none"> ▪ Cyclophosphamide ▪ Mycophenolate ▪ Azathioprine
Systemic lupus erythematosus (SLE)	<p>Ruxience (rituximab-pvvr) or Truxima (rituximab-abbs) may be considered medically necessary for the treatment of systemic lupus erythematosus (SLE) when:</p> <ul style="list-style-type: none"> • Used as add-on therapy therapy <p>AND</p>



Condition	Medical Necessity
Ruxience and Truxima are subject to review for site of service administration.	
	<ul style="list-style-type: none"> The individual has a diagnosis of SLE confirmed using either the American College of Rheumatology (ACR or EULAR/ACR) or Systemic Lupus International Collaborating Clinics (SLICC) criteria <p>AND</p> <ul style="list-style-type: none"> Has failed a 6-months trial of standard induction therapy with mycophenolate, cyclophosphamide, azathioprine, or other immunosuppressant, plus glucocorticoid
Systemic sclerosis (scleroderma)	<p>Ruxience (rituximab-pvvr) or Truxima (rituximab-abbs) may be considered medically necessary for the treatment of systemic sclerosis when:</p> <ul style="list-style-type: none"> Used for individuals refractory to first-line treatment with cyclophosphamide or glucocorticoids.
Autoimmune Dermatologic Diseases	
<p>Pemphigoid diseases:</p> <ul style="list-style-type: none"> Bullous pemphigoid Mucous membrane pemphigoid (including ocular cicatricial pemphigoid) Epidermolysis bullosa acquisita <p>Pemphigus diseases:</p> <ul style="list-style-type: none"> Pemphigus vulgaris Pemphigus foliaceus Paraneoplastic pemphigus 	<p>Ruxience (rituximab-pvvr) or Truxima (rituximab-abbs) may be considered medically necessary for the treatment of pemphigoid diseases in treatment-refractory individuals when:</p> <ul style="list-style-type: none"> Standard initial treatment was tried and failed. Standard initial treatment includes at least two of the following: <ul style="list-style-type: none"> Glucocorticoids, azathioprine, mycophenolate, or dapsone <p>Ruxience (rituximab-pvvr) or Truxima (rituximab-abbs) may be considered medically necessary as a first line treatment in patients newly diagnosed with a pemphigus disease.</p>
Hematologic	
<p>Autoimmune hemolytic anemias (AIHA)</p> <ul style="list-style-type: none"> Warm AHIA Cold AHIA 	<p>Ruxience (rituximab-pvvr) or Truxima (rituximab-abbs) may be considered medically necessary for the treatment of autoimmune hemolytic anemias (AIHA) when:</p> <ul style="list-style-type: none"> Used to treat warm AIHA in glucocorticoid-refractory or glucocorticoid-dependent patients <p>OR</p> <ul style="list-style-type: none"> Used to treat cold agglutinin disease (CAD)



Condition	Medical Necessity
Ruxience and Truxima are subject to review for site of service administration.	
Chronic graft-versus-host disease (GVHD)	<p>Ruxience (rituximab-pvvr) or Truxima (rituximab-abbs) may be considered medically necessary for the treatment of chronic GVHD when:</p> <ul style="list-style-type: none"> • Used in refractory to glucocorticoids
Desensitization of human leukocyte antigen (HLA)	<p>Ruxience (rituximab-pvvr) or Truxima (rituximab-abbs) may be considered medically necessary for renal transplant candidates when:</p> <ul style="list-style-type: none"> • Used in desensitization of HLA-sensitized renal transplant candidates prior to transplantation
Hemophilia	<p>Ruxience (rituximab-pvvr) or Truxima (rituximab-abbs) may be considered medically necessary in the treatment of hemophilia when:</p> <ul style="list-style-type: none"> • Used as a factor inhibitor for patients who are refractory to conventional first-line treatments (e.g., immune tolerance induction, glucocorticoids with or without cyclophosphamide). <p>AND</p> <ul style="list-style-type: none"> • Used as an add-on therapy
Idiopathic (immune) thrombocytopenic purpura (ITP)	<p>Ruxience (rituximab-pvvr) or Truxima (rituximab-abbs) may be considered medically necessary as second-line therapy for the treatment of ITP when:</p> <ul style="list-style-type: none"> • The individual's platelet counts continue to be at or less than 30,000 after first-line treatment using any one of the following: <ul style="list-style-type: none"> ○ IVIG ○ High-dose glucocorticoids ○ Anti-D immunoglobulin
Thrombotic thrombocytopenic purpura (TTP)	<p>Ruxience (rituximab-pvvr) or Truxima (rituximab-abbs) may be considered medically necessary for the treatment of TTP when:</p> <ul style="list-style-type: none"> • Used in individuals with refractory or relapsed disease (i.e., lack of response to plasma exchange therapy and glucocorticoids)
Other	
Multicentric Castleman disease (angiofollicular lymph node hyperplasia)	<p>Ruxience (rituximab-pvvr) or Truxima (rituximab-abbs) may be considered medically necessary for the treatment of multicentric Castleman disease.</p>



Second Line Products

Riabni (rituximab-arrx) and Rituxan (rituximab) are subject to review for site of service administration.

Second-line agents:

- Riabni (rituximab-arrx)
- Rituxan (rituximab)
- Rituxan Hycela (rituximab and hyaluronidase human)

Riabni (rituximab-arrx), Rituxan (rituximab-pvvr), and Rituxan Hycela (rituximab and hyaluronidase human) may be considered medically necessary as a second-line agent in the treatment of the indications listed below when:

- The individual has met the medical necessity criteria for the requested indication

AND

- Has had an inadequate response to or intolerance to Ruxience (rituximab-pvvr) or Truxima (rituximab-abbs)
 - **Exception:** An exception may be granted for Rituxan Hycela (rituximab and hyaluronidase human) when documentation is provided of difficult venous access.

Covered Indications:

- Autoimmune hemolytic anemias (AIHA)
- Chronic Graft-Versus-Host Disease
- Cryoglobulinemic Vasculitis Associated with Hepatitis-C Virus (HCV)
- Desensitization of Human Leukocyte Antigen (HLA)
- Eosinophilic granulomatosis with polyangiitis (Churg-Strauss Syndrome)
- Hemophilia
- Idiopathic Membranous Nephropathy
- Idiopathic Thrombocytopenic Purpura
- Lupus Nephritis
- Microscopic Polyangiitis
- Multicentric Castleman Disease
- Neuromyelitis Optica Spectrum Disorder (NMOSD)
- Pemphigoid Diseases
- Pemphigus Diseases
- Primary Sjögren Syndrome
- Rheumatoid Arthritis (RA)
- Systemic Lupus Erythematosus (SLE)
- Systemic Sclerosis (scleroderma)



Second Line Products

Riabni (rituximab-arrx) and Rituxan (rituximab) are subject to review for site of service administration.

- Thrombotic Thrombocytopenic Purpura (TTP)
- Wegener’s Granulomatosis

Drug	Investigational
<p>Rituximab Products</p>	<p>Rituximab is investigational for all other non-oncologic uses, including but not limited to:</p> <ul style="list-style-type: none"> • Induction immunosuppressive therapy for kidney transplantation • Induction immunosuppressive therapy for heart transplantation • Mixed connective tissue disease • Multiple sclerosis • Paroxysmal cold hemoglobinuria • Prophylaxis for graft-versus-host disease • Treatment of antibody-mediated rejection after pancreatic islet transplantation • Treatment of antibody-mediated rejection in solid organ transplant recipients • Treatment of minimal change disease • Treatment of myasthenia gravis <p>All other uses of rituximab products for conditions not outlined in this policy are considered investigational.</p> <p>The medications listed in this policy are subject to the product’s US Food and Drug Administration (FDA) dosage and administration prescribing information.</p>

Length of Approval	
Approval	Criteria
<p>Initial authorization</p>	<p>Non-formulary exception reviews for rituximab products listed in this policy may be approved up to 12 months.</p>



Length of Approval	
Approval	Criteria
	All other reviews for rituximab products listed in this policy may be approved up to 6 months.
Re-authorization criteria	Non-formulary exception reviews and all other reviews for rituximab products listed in this policy may be approved up to 12 months as long as the drug-specific coverage criteria are met and chart notes demonstrate that the individual continues to show a positive clinical response to therapy.

Documentation Requirements
<p>The individual’s medical records submitted for review should document that medical necessity criteria are met. The record should include clinical documentation of:</p> <ul style="list-style-type: none"> • Diagnosis/condition • History and physical examination documenting the severity of the condition • Prior treatment (if any) • If service is requested at an outpatient hospital-based setting, supporting documentation for why infusion cannot be performed at physician’s office, patient’s home, or an infusion center

Coding

Code	Description
HCPCS	
J3590	Unclassified biologics (use to report Amjevita , Cyltezo, Hyrimoz HCF, Sandoz, Simlandi)
J9311	Injection, rituximab 10 mg and hyaluronidase (Rituxan Hycela)
J9312	Injection, rituximab (Rituxan), 10 mg
Q5115	Injection, rituximab-abbs, biosimilar, (Truxima), 10mg
Q5119	Injection, rituximab-pvvr, biosimilar, (Ruxience), 10 mg
Q5123	Injection, rituximab-arrx, biosimilar, (Riabni), 10 mg



Dosing

Rituxan (rituximab) should be administered by a healthcare professional with appropriate medical support to manage severe and potentially fatal infusion reactions (Biogen & Genentech, 2020).

Pregnancy

Based on human data, rituximab can cause adverse developmental outcomes including B-cell lymphocytopenia in infants exposed to rituximab in-utero. In animal reproduction studies, intravenous administration of rituximab to pregnant cynomolgus monkeys during the period of organogenesis caused lymphoid B-cell depletion in the newborn offspring at doses resulting in 80% of the exposure (based on AUC) of those achieved following a dose of 2 grams in humans. Adverse outcomes in pregnancy occur regardless of the health of the mother or the use of medications. The background risk of major birth defects and miscarriage for the indicated populations is unknown. The estimated background risk in the US general population of major birth defects is 2%-4% and of miscarriage is 15%-20% of clinically recognized pregnancies. Advise pregnant women of the risk to a fetus.

Children

The age described in this policy for Site of Service reviews for medical necessity 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 pediatric unique physiology and psychology, this policy is limited to patients above the age of 13.



Description

Rituxan (rituximab) is a monoclonal antibody against the CD20 antigen on B lymphocytes. Rituximab lyses pre-B and B lymphocytes and is successfully used to treat B-cell lymphoma. Rituximab has been used with increased frequency for nononcologic indications, particularly autoimmune diseases thought to be B-cell mediated.

Background

Rituxan (rituximab)

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

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

Rituximab is infused intravenously.

Adverse Events

Rituxan (rituximab) carries the following black box warnings²:

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

- Progressive multifocal leukoencephalopathy resulting in death

Labelled warnings and precautions include:

- Tumor lysis syndrome (for patients with hematologic malignancies)
- Infections
- Cardiac arrhythmias and angina
- Renal toxicity
- Bowel obstruction and perforation
- Not administering live virus vaccines before or during rituximab therapy
- Embryo-fetal toxicity

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.

Summary of Evidence

Food and Drug Administration–Approved Uses

Rheumatoid Arthritis (FDA label)

For individuals who have moderately to severely active rheumatoid arthritis and inadequate response to one or more standard agents (eg, tumor necrosis factor inhibitors, inadequate response to methotrexate or other conventional synthetic disease-modifying antirheumatic drug) who receive rituximab and methotrexate, the evidence includes 4 RCTs and observational studies. Relevant outcomes are symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. Compared with methotrexate alone, rituximab improved disease-related outcomes consistent with an improved benefit-risk profile. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.



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. Observational studies have suggested switching to rituximab after failing 1 TNF inhibitor may be more efficacious than switching to another TNF inhibitor. Evidence for the use of rituximab in TNF inhibitor–naïve patients is lacking. For patients with an inadequate response to MTX and contraindications to TNF inhibitor therapy, rituximab may be a reasonable option. In the 5-year extension study, adverse event rates were generally stable over time.

Antineutrophil Antibody –Associated Vasculitides (Granulomatosis with polyangiitis and microscopic polyangiitis)- (FDA Label)

Granulomatosis with polyangiitis (GPA; Wegener granulomatosis), 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 proteinase 3 (PR3) or myeloperoxidase (MPO), enzymes found in neutrophil granulocytes.¹⁵² 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 are also considered pauci-immune because, unlike immune complex vasculitides, they are not characterized by immune complex deposition.¹⁵³ 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.¹⁵⁴ Limited vasculitis may respond to MTX plus glucocorticoids; standard treatment for more severe disease is cyclophosphamide plus glucocorticoids. Finally, these conditions are uncommon. The prevalence of GPA in the United States is estimated at 32 per million and MPA 2.9 per million.¹⁵⁵

For individuals who have antineutrophil cytoplasmic antibody–associated vasculitides (granulomatosis with polyangiitis and microscopic polyangiitis) who receive rituximab and glucocorticoids, the evidence includes evidence from 3 RCTs and observational studies. Relevant outcomes are symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. Compared with a cyclophosphamide regimen, rituximab improved disease-related outcomes consistent with an improved benefit-risk profile (this was accomplished over the course of two trials). In 1 trial, rituximab maintenance was superior to an azathioprine regimen but accompanied by considerable uncertainty. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.



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 serious adverse events at 12 months in patients treated with or without a rituximab-containing induction regimen. One trial found rituximab of similar efficacy in maintaining remission compared with an azathioprine regimen.

Pemphigoid and Pemphigus Diseases (FDA Label)

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.¹⁵⁶

The evidence on first-line treatment with rituximab plus corticosteroids in patients with newly diagnosed pemphigus consists of an RCT and small case series. The RCT found that patients treated with rituximab plus short-term corticosteroids (3-6 months) had significantly better outcomes than those treated with long-term corticosteroid use. Outcomes included the complete response rate, cumulative dose of corticosteroids, and rate of grade 3 or 4 serious adverse events.

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 (e.g.,



blindness) or death, reported response rates were high, and treatment options in refractory patients are limited. For these reasons, rituximab may be considered medically necessary for treatment of the pemphigoid and pemphigus diseases reviewed in the literature in treatment-refractory patients.

Food and Drug Administration–Off-Label Covered Uses

Hematologic Disorders and Vasculitides

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 react 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. Glucocorticoids and splenectomy are currently used to treat AIHA refractory to first-line therapy. Corticosteroids are first-line treatment in warm AIHA but less effective in cold AIHA.^{3,4}

Rituximab is not considered a treatment option for paroxysmal cold hemoglobinuria due to the generally self-limiting course and excellent prognosis of this disorder.

For individuals who have AIHA—warm AIHA and cold agglutinin syndrome—refractory to first-line therapy who receive rituximab, the evidence includes RCTs and observational studies. Relevant outcomes are symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. Two RCTs have found that overall response rates were better with rituximab than a control condition at 1 year in patients with newly diagnosed warm AIHA. Serious adverse events were higher with rituximab than corticosteroids (1 RCT) but lower than placebo (the other RCT). Response rates from observation studies have supported these findings and found lesser yet substantive response rates in patients with cold agglutinin syndrome. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.



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, intravenous 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, especially in children.^{10,11} For individuals who have relapsed or refractory ITP who receive rituximab, the evidence includes an RCT of second-line therapy and observational studies. Relevant outcomes are symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. Rituximab as second-line treatment for adult thrombocytopenia trial failed to demonstrate improved outcomes with rituximab as second-line therapy in adults with ITP. The evidence is insufficient to determine the effects of the technology on health outcomes.

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).¹⁵ TTP is due to an acquired (95% of cases) or congenital (5% of cases) deficiency of the von Willebrand factor–cleaving protease, ADAMTS13. In 38% to 95% of cases of idiopathic TTP, anti-ADAMTS13 neutralizing antibodies are present.¹⁶ When ADAMTS13 is absent or depleted, large uncleaved von Willebrand factor multimers aggregate in high shear areas of the microvasculature, leading to thrombotic microangiopathy.¹⁷ The main 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.¹⁸ For these patients, increased PE and/or addition of cyclosporine are current treatment options.¹⁷

For individuals who have relapsed or refractory TTP who receive rituximab, the evidence includes a nonrandomized trial (phase 2), a cohort study, and case series. Relevant outcomes are symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. These studies have provided consistent evidence of improved health outcomes. For example, a phase 2 trial reported substantially lower relapse rates than historical controls. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.



Factor Inhibitors in Hemophilia

Hemophilia is a coagulopathy characterized by reduced, absent, or nonfunctioning clotting factor VIII (FVIII) (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.²⁸ If left untreated, antibody inhibitors eventually render replacement therapy ineffective. Immune tolerance induction (ITI) is recommended first-line treatment of factor inhibitors in hemophilia.³⁰ ITI comprises increasing the dose and frequency of factor infusions until inhibitor is undetectable and FVIII levels normalize. Success rate is low (25%), and associated risks (e.g., anaphylaxis, irreversible nephrotic syndrome) are significant. Immunosuppressive therapy with corticosteroids alone or in combination with cyclophosphamide is recommended for first-line inhibitor eradication. 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 auto-antibodies against FVIII. 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.²⁹

For individuals who have congenital or acquired hemophilia A with inhibitory antibodies, refractory to first-line therapy, who receive rituximab, the evidence includes a phase 2 trial, a cohort study, and case series. Relevant outcomes are symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. Response rates have varied among reports (25% to 50%), depending on whether rituximab was administered as mono- or combination therapy; remission rates have generally been high. Treatment-related adverse events—some severe—have been reported. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Autoimmune-Related Connective Tissue Disorders

Mixed Connective Tissue Disease

Mixed connective tissue disease (MCTD) has various features of systemic lupus erythematosus (SLE), systemic sclerosis, polymyositis/dermatomyositis (PM/DM), and rheumatoid arthritis (RA) in the presence of increased anti-ribonucleoprotein (anti-RNP) antibodies.⁴¹ Although some have questioned 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, systemic sclerosis, 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.

For individuals who have MCTD who receive rituximab, the evidence includes 2 case series. Relevant outcomes are symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. In one of the series, 3 of 5 patients with MCTD achieved partial remission with rituximab and, in the other, which focused on MCTD related to interstitial lung disease, there was no significant change in forced vital capacity at 1 or 2 years after initiating rituximab. The evidence is insufficient to determine the effects of the technology on health outcomes.

Multicentric Castleman Disease

Castleman disease (angiofollicular lymph node hyperplasia) is a rare lymphoproliferative disorder associated with human herpes virus-8 infection. Prevalence is increased among HIV-infected patients and associated with Kaposi sarcoma. Progression to lymphoma and mortality is high in these patients. Castleman disease has two distinct forms with characteristic findings on histologic examination: unicentric or localized (hyaline vascular histology), and multicentric (plasma cell infiltrate). The clinical presentation typically involves lymphadenopathy and multiorgan involvement with an aggressive course. In HIV-non-infected patients, multicentric Castleman disease typically presents after age 70 years.⁴⁴ 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.⁴⁵ Other treatments include combination chemotherapy and tocilizumab, a monoclonal anti-interleukin 6 antibody.

For individuals who have multicentric Castleman disease (angiofollicular lymph node hyperplasia) who receive rituximab, the evidence includes 2 prospective and 3 retrospective cohort studies. Relevant outcomes are symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. Although the evidence base consists of nonrandomized studies, rituximab has significantly improved overall survival and markedly reduced the incidence of non-Hodgkin lymphoma. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.



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. Therapies that are currently being used to treat Sjögren syndrome include MTX, hydroxychloroquine, infliximab, etanercept, azathioprine, mycophenolate mofetil (MMF), cyclophosphamide, and glucocorticoids.

For individuals who have primary Sjögren syndrome, refractory to first-line therapy, who receive rituximab, the evidence includes a large RCT (disease onset < 10 years prior) and smaller observational studies. Relevant outcomes are symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. The efficacy of rituximab has not been consistently demonstrated in this population. For example, a large (N=120) randomized trial showed no difference in response rates compared with placebo, and a small (N=41) nonrandomized trial showed statistically significant differences in response rates compared with disease-modifying antirheumatic drugs in previously treated patients. The incidence of adverse events did not appear to increase above that observed in other patient populations. The evidence is insufficient to determine the effects of the technology on health outcomes.

Systemic Lupus Erythematosus

For individuals who have SLE, refractory to first-line therapy, who receive rituximab, the evidence includes a large RCT and systematic reviews that also included observational studies. Relevant outcomes are symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. The single RCT failed to show improved response rates at 1 year with rituximab add-on therapy. Cohort studies and case series of refractory patients have generally reported higher response rates than controlled studies. Therapies currently being used to treat SLE refractory to first-line therapy include MTX, hydroxychloroquine, belimumab, etanercept, azathioprine, MMF, cyclophosphamide, cyclosporine, and glucocorticoids. The evidence is insufficient to determine the effects of the technology on health outcomes.



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.⁶⁵ Estimated 5-year survival among patients with International Society of Nephrology/Renal Pathology Society class IV (diffuse) LN is 80% and among all SLE patients, 86%⁶⁶; 5% to 10% of LN patients will progress to end-stage renal disease at 10 years.⁶⁷ Therapies currently being used to treat lupus nephritis include glucocorticoids, cyclophosphamide, MMF, cyclosporine, tacrolimus, and belimumab. Treatment regimens including cyclophosphamide or MMF are administered with corticosteroids. Response rates at 1 year are 50% to 80%, but they are often only partial responses.

For individuals who have lupus nephritis, refractory to first-line therapy, who receive rituximab, the evidence includes an RCT and noncomparative studies. Relevant outcomes are symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. The single RCT did not show improved response rates at 1 year with rituximab add-on therapy. Noncomparative studies have reported complete and partial response rates of 30% to 40% and approximately 35%, respectively, in patients with mostly refractory disease. Adverse events occurred in approximately 20% of patients. The evidence is insufficient to determine the effects of the technology on health outcomes.

Systemic Sclerosis (Scleroderma)

The purpose of rituximab in patients who have systemic sclerosis (scleroderma), refractory to first-line therapy, is to provide a treatment option that is an alternative to or an improvement on existing therapies. Therapies that are currently being used to treat systemic sclerosis include MMF, cyclophosphamide, and cyclosporine. For individuals who have systemic sclerosis, refractory to first-line therapy, who receive rituximab, the evidence includes observational studies and a small, unblinded trial. Relevant outcomes are symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. Add-on rituximab therapy has generally improved skin symptoms and pulmonary function tests; adverse events, including sepsis deaths, occurred in 21% to 47% of patients. Long-term follow-up for efficacy and safety is limited. The evidence is insufficient to determine the effects of the technology on health outcomes.



Other Autoimmune-Related Conditions and Disorders

Churg-Strauss Syndrome

Churg-Strauss syndrome, also called eosinophilic granulomatosis with polyangiitis (EGPA), is an anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis characterized by peripheral and tissue eosinophilia, frequently affecting the lungs, in patients with asthma.²¹ The disease is uncommon, with an estimated prevalence of 11 to 14 per million adults. 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 granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA), rituximab has been used in patients with EGPA syndrome refractory to conventional immunosuppressant therapy.²²

For individuals who have Churg-Strauss syndrome (eosinophilic granulomatosis with polyangiitis) who receive rituximab, the evidence includes a single-center retrospective observational study and 3 case series. Relevant outcomes are symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. Response and remission rates have generally been high, but treatment-related adverse events—some severe—have been reported. The evidence is insufficient to determine the effects of the technology on health outcomes.

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 is the treatment of choice. For patients who do not achieve sustained viral response, corticosteroids and cytotoxic agents are alternative treatment options but may exacerbate underlying liver disease.^{34,35}

For individuals who have HCV-associated cryoglobulinemic vasculitis who receive rituximab, the evidence includes 2 RCTs, a phase 2 nonrandomized trial, and observational studies. Relevant outcomes are symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. The reported response rates in these studies are consistent with



improved health outcomes. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Multiple Sclerosis

The purpose of rituximab in patients who have multiple sclerosis (MS) is to provide a treatment option that is an alternative to or an improvement on existing therapies. Therapies that are currently being used to treat MS include interferons, glatiramer acetate, teriflunomide, fingolimod, dimethyl fumarate, alemtuzumab, mitoxantrone, and natalizumab.

For individuals who have MS who receive rituximab, the evidence includes 2 RCTs, a registry study, and case series. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. One RCT in patients with relapsing-remitting MS showed reductions in the number of lesions detected by gadolinium-enhanced magnetic resonance imaging at 24 and 48 weeks, and in clinical outcomes at 24-week follow-up. However, methodologic limitations restrict the conclusions drawn from these data. One well-designed RCT in patients with primary-progressive MS demonstrated no effect of rituximab on disease progression. A large registry study found that rituximab was associated with a relatively low rate of adverse events and relapses and little change in disability scores; this study lacked a comparison group. The evidence is insufficient to determine the effects of the technology on health outcomes.

Neuromyelitis Optica

Neuromyelitis optica (NMO) is a rare autoimmune inflammatory disorder that selectively affects the spinal cord and optic nerves; clinical presentation is characterized by severe optic neuritis that can lead to blindness and transverse myelitis that can lead to paralysis. The clinical course typically is more severe than in MS, and often fatal,⁹⁷ and treatments may differ.^{98,99} An autoantibody to aquaporin-4, a water channel found in high concentrations at the blood-brain barrier, is included in NMO diagnostic criteria.^{100,101} Curative treatment does not currently exist; treatment goals are: relapse remission, relapse prevention, and symptom relief.¹⁰²

Immunosuppression with azathioprine or mycophenolate mofetil (MMF) is commonly used for relapse prevention. Therapies currently used to treat NMO include azathioprine, MMF, methotrexate, mitoxantrone, and glucocorticoids. Rituximab is being studied for relapse prevention in NMO.



For individuals who have NMO (prevention relapse), refractory to first-line therapy, who receive rituximab, the evidence includes uncontrolled observational studies and systematic reviews. Relevant outcomes are symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. A 2016 systematic review of 46 uncontrolled studies found significant reductions in the relapse rate and Expanded Disability Status Scale scores after beginning treatment with rituximab. Based on adverse events reported, the safety of rituximab in NMO appeared comparable to the safety in other patient populations. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Myasthenia Gravis

Myasthenia gravis is a chronic autoimmune disorder that affects the neuromuscular junction resulting in varying degrees of muscular weakness. The normal communication of nerve impulses involves nerve endings releasing acetylcholine, a neurotransmitter at the neuromuscular junction, which normally binds with acetylcholine receptors that activate and result in a muscle contraction. For individuals with myasthenia gravis, this cholinergic communication is disrupted by antibodies.

For individuals who have refractory and nonrefractory myasthenia gravis who receive rituximab, the evidence includes observational studies and a systematic review. Relevant outcomes are change in disease status, quality of life, and treatment-related morbidity. A systematic review found a significant reduction in a myasthenia gravis symptom score after beginning rituximab treatment and a relatively low rate of adverse events. A limitation of the studies was that adverse event reports were not available for all patients. An uncontrolled observational study found significantly better clinical outcomes in patients with anti-MuSK myasthenia who were treated with rituximab compared with those who did not receive rituximab. However, few controlled studies and no RCTs are available. The evidence is insufficient to determine the effects of the technology on health outcomes.

Idiopathic Membranous Nephropathy

Membranous nephropathy involves the abnormal thickening of the glomerular basement membrane and is a leading cause of nephrotic syndrome. Most membranous nephropathy cases occur from unknown causes, and secondary membranous nephropathy may result from other predisposing diseases, infection, or medical therapy. In many cases, conservative treatment with renin-angiotensin system blockade is provided. Immunomodulatory therapies (e.g., alkylating



agents, calcineurin inhibitors, corticosteroids) are used to treat individuals who are unresponsive to conservative therapy. Rituximab has been evaluated in patients with idiopathic membranous nephropathy who have failed previous treatment with other immunosuppressive regimens or those with a moderate risk of progression who have not previously received immunosuppressive therapy.

For individuals who have idiopathic membranous nephropathy who receive rituximab, the evidence includes an RCT and observational studies. Relevant outcomes are change in disease status, quality of life, and treatment-related morbidity. Rituximab may have moderate benefit in patients with idiopathic membranous nephropathy who have failed previous treatment with other immunosuppressive regimens or those with a moderate risk of progression who have not previously received immunosuppressive therapy. However, an RCT with longer follow-up is needed to confirm the benefits of rituximab and to determine the optimal schedule, dose, and long-term safety and efficacy. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Minimal Change Disease

For individuals who have minimal change in disease (adults and children) who receive rituximab, the evidence includes observational studies in adults and 2 RCTs and observational studies in children. Relevant outcomes are change in disease status, quality of life, and treatment-related morbidity. Rituximab benefit children with nephrotic syndrome associated with minimal change disease. However, because of the risk of severe and potentially life-threatening complications, rituximab use should be restricted to children with frequent relapses and serious adverse events from their medications (because the long-term efficacy and safety of rituximab in this group of patients remain unclear). The evidence is insufficient to determine the effects of the technology on health outcomes.

Transplant-Related Conditions and Disorders

Glucocorticoid-Refractory Chronic Graft-Versus-Host Disease (GVHD)

Chronic GVHD, historically defined as occurring more than 100 days after transplant,¹²⁸ is the primary cause of late morbidity and mortality after allogeneic hematopoietic cell transplantation.¹²⁹ Approximately half of the patients respond to first-line treatment (systemic corticosteroid with or without a calcineurin inhibitor), but treatment options for steroid-refractory disease are limited, and the prognosis is poor. Therapies currently being used to treat



glucocorticoid-refractory chronic GVHD include MMF, cyclophosphamide, and cyclosporine. For individuals who have corticosteroid-refractory chronic GVHD who receive rituximab, the evidence includes multiple cohort studies. Relevant outcomes are change in disease status, quality of life, and treatment-related morbidity. Treatment with rituximab has demonstrated response rates in most patients, with sustained response and steroid reduction or discontinuation in some. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Pretransplant HLA Desensitization in Kidney Transplantation.

Patients who are HLA-sensitized have broadly reactive alloantibodies (e.g., due to previous pregnancy, transfusion of blood or blood products, or transplantation). HLA-sensitized patients are difficult to match for donor organs because of the high risks of hyperacute rejection and graft loss with cross-matched organs (i.e., positive for reactive antigens). Panel reactive antibody (PRA) assays define the level of HLA sensitization and are used to optimize identification of compatible donors. Some transplant centers employ desensitization protocols to overcome HLA sensitization. Protocols commonly use low-dose IVIG with PE or high-dose IVIG.¹³⁵

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, therefore this is a covered indication.

Kidney and Heart Transplant Candidates Receiving Induction Immunosuppression

Antibodies other than anti-HLA antibodies that are circulating in the planned transplant recipient may cause damage to the donor organ. Antibody-mediated injury to allografts comprises ABMR, ABMR without complement deposition, antibody-mediated endarteritis, and accelerated arteriosclerosis of allografts.¹⁴¹ Induction immunosuppressive regimens initiated before, at the time of, or immediately after transplantation, mute T-cell responses to antigen presentation reduces acute rejection.¹⁴² Therapies that are currently being used to treat patients with heart or kidney transplant who are receiving induction include immunosuppressive antibodies, basiliximab, and alemtuzumab. Rituximab as part of a combination induction regimen that typically includes plasmapheresis and IVIG therapy such as antithymocyte globulin recessive agents is being considered.



For individuals who are kidney transplant candidates who are receiving induction immunosuppressive therapy, the evidence includes cohort studies with historical controls and case series RCTs and systematic reviews. Although observed improvements in outcomes have suggested potential benefit with rituximab, data are retrospective or from small prospective studies. Dose-response studies and larger RCTs with longer follow-up are needed to demonstrate improved health outcomes. For individuals who are heart transplant candidates who are receiving induction immunosuppressive therapy, the recommendation for the use of rituximab as part of a combination regimen is based on consensus reporting of case reports and expert opinion.

Antibody-Mediated Rejection of a Solid Organ Transplant

Therapies currently being used to treat patients with ABMR of a solid organ transplant include immunosuppression, plasmapheresis or PE, IVIGs, corticosteroids, and antilymphocyte antibodies. For individuals who have ABMR of a solid organ transplant who receive rituximab, the evidence includes cohort studies with historical controls and case series. Relevant outcomes are change in disease status, quality of life, and treatment-related morbidity. Although observed improvements in outcomes have suggested potential benefit with rituximab, data are retrospective or from small prospective studies. Dose-response studies and larger RCTs with longer follow-up are needed to demonstrate improved health outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

ABMR After Pancreatic Islet Transplantation Autoimmune destruction of insulin-secreting islet beta-cells causes type 1 diabetes.¹⁵¹ 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.¹⁵² Pancreatic islet transplantation is used in patients who have type 1 diabetes complicated by recurrent severe hypoglycemic episodes, and insulin independence is restored in 44% of patients.¹⁵³ However, graft function commonly declines over time, which is thought to be due in part to allograft rejection. Immunosuppression management after islet transplantation is not standardized. Therapies currently being used to treat ABMR after pancreatic islet cell transplantation include corticosteroids.

For individuals who have ABMR after pancreatic islet transplantation who receive rituximab, the evidence includes a case report. Relevant outcomes are change in disease status, quality of life, and treatment-related morbidity. The evidence is insufficient to determine the effects of the technology on health outcomes.



Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in [Table 1](#).

Table 1. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Warm autoimmune hemolytic anemia			
NCT01181154^a	Rituximab in Adult's Warm Auto-Immune Hemolytic Anemia: a Phase III, Double-blind, Randomised Placebo-controlled Trial	32	Jan 2016 (completed; unpublished)
Churg-Strauss syndrome			
NCT02807103	Evaluation of Rituximab-based Regimen Compared to Conventional Therapeutic Strategy For Remission Induction in Patients With Newly-Diagnosed or Relapsing Eosinophilic Granulomatosis With Polyangiitis. Prospective, Randomized, Controlled, Double-blind Study	107	Oct 2020 (completed; unpublished)
NCT03164473	MAINTenance of Remission With RITuximab Versus Azathioprine for Patients With Newly-diagnosed or Relapsing Eosinophilic Granulomatosis With Polyangiitis. A Prospective, Randomized, Controlled, Double-blind Study: the MAINRITSEG Trial	98	Oct 2024 (active)
Systemic sclerosis			
NCT01748084	Evaluation of Rituximab in Systemic Sclerosis Associated Polyarthritis (RECOVER)	22	Apr 2016 (completed)
Myasthenia gravis			
NCT06342544	Immediate Corticosteroid Therapy and Rituximab to Prevent Generalization in Ocular Myasthenia: a PROBE Multicenter Open-label Randomized Controlled Trial. (IMCOMG)	128	Jun 2029
NCT05332587	Efficacy and Safety of Low-dose Rituximab in the Treatment of Refractory Myasthenia Gravis	50	Jul 2022 (completed; unpublished)
Idiopathic membranous nephropathy			
NCT01955187	European Multicenter and Open-Label Controlled Randomized Trial to Evaluate the Efficacy of Sequential Treatment With Tacrolimus-Rituximab Versus Steroids Plus Cyclophosphamide in Patients With Primary Membranous Nephropathy (The STARMEN Study)	86	June 2019 (completed)



NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT03018535	A Randomized Controlled Trial of Rituximab Versus Steroids and Cyclophosphamide in the Treatment of Idiopathic Membranous Nephropathy (RI-CYCLO)	76	Dec 2019
Human leukocyte antigen sensitization pretransplant			
NCT01095172 ^a	A Randomized Trial of Rituximab in Induction Therapy for Living Donor Renal Transplantation	100	Oct 2022 (active)
Lupus Nephritis			
NCT05207358	Minimizing Glucocorticoid Administration in Patients With Proliferative Lupus Nephritis During the Induction of Remission Period-EUROLUPUS vs. RITUXILUP Regimen: A Randomized Study	30	Dec 2028

ANCA: antineutrophil cytoplasmic antibody; NCT: national clinical trial.

^a Industry sponsored or co-sponsored.

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.

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 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, immunoglobulin M-related demyelinating neuropathies, myasthenia gravis, Lambert-Eaton myasthenic syndrome, ABO incompatible organ/tissue grafts, and post-solid organ transplant membranous nephropathy.



Practice Guidelines and Position Statements

American College of Rheumatology

The American College of Rheumatology (2012) published evidence-based consensus guidelines on the treatment of lupus nephritis.¹⁵⁷ 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).

Rheumatoid Arthritis

The American College of Rheumatology updated its evidence-based consensus guidelines on rheumatoid arthritis (RA) in 2015 (updated guideline anticipated in 2021) and made the following recommendations¹⁶³:

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

In 2020, the ACR published guidelines for the management of pulmonary disease in patients with Sjögren syndrome. The following recommendations were made regarding the use of rituximab in this setting:

- "If initial treatment with MMF [mycophenolate mofetil] or azathioprine is insufficient or not tolerated in Sjögren's patients with interstitial lung disease (ILD) who are symptomatic and in whom pulmonary function tests (PFTs) or high-resolution CT [computed tomography] (HRCT) demonstrated moderate-severe impairment, subsequent second-line maintenance drugs may include rituximab and calcineurin inhibitors, cyclosporine, or tacrolimus." (Strength of Evidence: low; Strength of Recommendation: weak)
- "In a Sjögren's patient with ILD who has acute or subacute hypoxic respiratory failure requiring hospitalization, despite initial therapies, rituximab or cyclophosphamide should be considered in addition to high-dose corticosteroids." (Strength of Evidence: low; Strength of Recommendation: moderate)

An updated guideline covering recommendations for all ILDs was published in 2023. Rituximab was conditionally recommended for patients with systemic autoimmune rheumatic disease-ILD as a first-line treatment option and for those with progression despite first-line ILD treatment. Rituximab was also conditionally recommended for patients with rapidly progressive systemic autoimmune rheumatic disease-ILD.

The 2021 ACR/Vasculitis Foundation guideline for the management of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis recommends rituximab in the setting of severe granulomatosis with polyangiitis and microscopic polyangiitis, but not specifically eosinophilic granulomatosis with polyangiitis.



American Society of Hematology

The American Society of Hematology (2019) published evidence-based guidelines on immune thrombocytopenia (ITP).¹⁵⁸ Rituximab was suggested in the following clinical scenarios (all are conditional recommendations which “the guideline panel suggests...”):

- “In adults with newly diagnosed ITP, the ASH guideline panel suggests corticosteroids alone rather than rituximab and corticosteroids for initial therapy”
- “In adults with ITP lasting ≥ 3 months who are corticosteroid-dependent or have no response to corticosteroids, the ASH guideline panel suggests rituximab rather than splenectomy”
- “In adults with ITP lasting ≥ 3 months who are corticosteroid-dependent or have no response to corticosteroids, the ASH guideline panel suggests a TPO-RA rather than rituximab”
- “In children with ITP who have non–life-threatening mucosal bleeding and/or diminished HRQoL and do not respond to first-line treatment, the ASH guideline panel suggests the use of TPO-RAs rather than rituximab”
- “In children with ITP who have non–life-threatening mucosal bleeding and/or diminished HRQoL and do not respond to first-line treatment, the ASH guideline panel suggests rituximab rather than splenectomy”

American Thoracic Society

In 2023, the American Thoracic Society (ATS) published guidelines for the treatment of systemic sclerosis-associated ILD (SSc-ILD). The authors provided a conditional recommendation for the use of rituximab (among other immunosuppressants) based on very low-quality evidence. Authors also noted that: “Further research is needed to determine the most optimal timing for the use of rituximab in the disease course of SSc-ILD (eg, in patients with an initial diagnosis of SSc-ILD vs. in stable SSc-ILD vs. progressive SSc-ILD).”

International Society of Heart and Lung Transplantation

In 2010, the International Society of Heart and Lung Transplantation (ISHLT) published evidence-based consensus guidelines on the care of heart transplant recipients. These guidelines were updated in 2022. Per the updated guidelines, rituximab was recommended for:



- Desensitization therapy in human leukocyte antigen-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).
- Preoperatively if isohemagglutinin titers >1:32 or added post operatively in cases of increasing isohemagglutinin levels (class 2a recommendation, weight of evidence/opinion favors usefulness/efficacy; level C evidence)

The guidelines also stated that at this time, routine rituximab induction cannot be recommended in non-sensitized cardiac transplant recipients.

In 2018, the ISHLT published a consensus document on the management of antibodies in heart transplantation. Rituximab was suggested as a treatment option for sensitized patients awaiting heart transplantation.

National Institute for Health and Care Excellence

Multiple Sclerosis (MS)

The National Institute for Health and Care Excellence (2022) updated its guidance on the management of multiple sclerosis in primary and secondary care.¹⁵⁹ The guidance did not include rituximab.

ANCA-Associated (Pauci-Immune) Glomerulonephritis

In 2014, the National Institute for Health and Care Excellence issued guidance rituximab in combination with glucocorticoids for treating antineutrophil cytoplasmic antibody-associated vasculitis.^{16,4}

Rituximab, in combination with glucocorticoids, is recommended as an option for inducing remission in adults with anti-neutrophil cytoplasmic antibody [ANCA]-associated vasculitis (severely active granulomatosis with polyangiitis [Wegener's] and microscopic polyangiitis), only if:

further cyclophosphamide treatment would exceed the maximum cumulative cyclophosphamide dose or cyclophosphamide is contraindicated or not tolerated or the



person has not completed their family and treatment with cyclophosphamide may materially affect their fertility or the disease has remained active or progressed despite a course of cyclophosphamide lasting 3–6months or the person has had uroepithelial malignancy.

The guidance did not offer conclusions on maintenance therapy.

British Committee for Standards in Haematology

Thrombotic Thrombocytopenic Purpura

The British Committee for Standards in Haematology (BCSH) published evidence-based consensus guidelines for treatment of TTP and thrombotic microangiopathy in 2012.⁶ 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:

Table 2. BCSH Recommendations on Treatment of Thrombotic Thrombocytopenic Purpura

Recommendations	LOE	SOR
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 Ideally plasma exchange should be withheld for at least 4 hours after completing a rituximab infusion	1B	Strong
Increased plasma exchange and/or rituximab therapy are the agents of choice in refractory or relapsing disease	1B	Strong
In patients in remission who have a documented reduction of ADAMTS13 activity to <5%, elective therapy with rituximab can be considered	1B	Strong
In resistant HIV-related TTP, rituximab could be considered	2B	Weak

LOE: level of evidence; SOR: strength of recommendation; TTP: thrombotic thrombocytopenic purpura.

MS Coalition

In June 2019, a consensus paper was updated by the MS Coalition that discusses the use of disease-modifying therapies in MS. Rituximab is listed among various options, involving



different mechanisms of action and modes of administration, which have shown benefits in patients with MS.

American Academy of Neurology

Multiple Sclerosis

The American Academy of Neurology (2018) updated its guidelines on disease-modifying therapies for adults with multiple sclerosis.¹⁶⁰ For patients with relapse-remitting multiple sclerosis, rituximab was judged to be likely more effective than placebo regarding the decreased risk of relapse at 1 year, as well as the decreased volume of T2 lesions from baseline to week 36, with a moderate confidence in the evidence (1 class II study). However, the evidence on the efficacy of rituximab in decreased annualized relapse rate at 1 year compared with placebo was insufficient (very low confidence in the evidence). The evidence is also insufficient regarding adverse event-related withdrawal and infection-associated serious adverse events following rituximab vs placebo (very low confidence in the evidence). For patients with progressive multiple sclerosis, rituximab was not found to be more effective than placebo in reducing the risk of disease progression over 2 years (low confidence in the evidence). Overall, the American Academy of Neurology recommended that clinicians counsel patients considering rituximab or other immunosuppressive agents regarding treatment risks (level B recommendation).

National Multiple Sclerosis Society

The National Multiple Sclerosis Society does not include rituximab among its listed treatments for MS.¹⁶⁵

Neuromyelitis Optica Study Group

Neuromyelitis Optica

The Neuromyelitis Optica Study Group (2014) published evidence-based consensus recommendations on the diagnosis and treatment of neuromyelitis optica.¹⁰² Rituximab was recommended as first-line treatment, along with azathioprine, and as second-line treatment after azathioprine failure.



International Society of Heart and Lung Transplantation

The International Society of Heart and Lung Transplantation (2010) published evidence-based consensus guidelines for the care of heart transplant recipients.¹⁴⁵ Rituximab was recommended for:

- Desensitization therapy in human leukocyte antigen–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)

In 2018, the International Society of Heart and Lung Transplantation published a consensus document on the management of antibodies in heart transplantation. Rituximab was suggested as a treatment option for sensitized patients awaiting heart transplantation.¹⁶²

International Society of Thrombosis and Haemostasis

In 2020, the International Society on Thrombosis and Haemostasis (ISTH) published guidelines for the treatment of thrombotic thrombocytopenic purpura (TTP). The following recommendations were made regarding the use of rituximab in immune-mediated TTP (iTTP):

- "For patients with iTTP experiencing their first acute event, the panel suggests the addition of rituximab thrombotic thrombocytopenic purpura to corticosteroids and therapeutic plasma exchange (TPE) over corticosteroids and TPE alone. (A conditional recommendation in the context of very low certainty evidence.)"
- "For patients with iTTP experiencing a relapse, the panel suggests the addition of rituximab to corticosteroids and TPE over corticosteroids and TPE alone. (A conditional recommendation in the context of very low certainty evidence.)"
- "For patients with iTTP who are in remission, but still have low plasma ADAMTS13 activity with no clinical signs/symptoms, the panel suggests the use of rituximab over nonuse of rituximab for prophylaxis. (A conditional recommendation in the context of very low certainty evidence.)"



Kidney Disease and Improving Global Outcomes

The Kidney Disease and Improving Global Outcomes (KDIGO) guideline for the management of glomerular diseases was published in October 2021. The guideline made the following relevant recommendations for glomerular diseases:

Membranous nephropathy

- "For patients with MN [membranous nephropathy] and at least one risk factor for disease progression, we recommend using rituximab or cyclophosphamide and alternate month glucocorticoids for 6 months, or CNI [calcineurin inhibitor]-based therapy for ≥ 6 months, with the choice of treatment depending on the risk estimate."

Nephrotic syndrome

- "For children with frequently relapsing nephrotic syndrome who develop serious glucocorticoid-related adverse effects and for all children with steroid-dependent nephrotic syndrome, we recommend that glucocorticoid-sparing agents be prescribed, rather than no treatment or continuation with glucocorticoid treatment alone...Patients should ideally be in remission with glucocorticoids prior to the initiation of glucocorticoid sparing agents such as oral cyclophosphamide, levamisole, mycophenolate mofetil (MMF), rituximab, or calcineurin inhibitors (CNIs). Coadministration of glucocorticoids is recommended for ≥ 2 weeks following initiation of glucocorticoid-sparing treatment... Choosing the most appropriate glucocorticoid-sparing agent from among oral cyclophosphamide, levamisole, MMF, rituximab, and CNI is a decision that requires careful consideration of specific patient related issues such as resources, adherence, adverse effects, and patient preferences. Oral cyclophosphamide and levamisole may be preferable glucocorticoid-sparing therapies in frequently relapsing nephrotic syndrome. MMF, rituximab, CNIs, and to a lesser extent, oral cyclophosphamide may be preferable to glucocorticoid-sparing therapies in children with steroid-dependent nephrotic syndrome."

Minimal change disease

- "We recommend cyclophosphamide, rituximab, CNIs, or mycophenolic acid analogs (MPAA) for the treatment of frequently relapsing/steroid-dependent MCD [minimal change disease], rather than prednisone alone or no treatment."

A KDIGO guideline for the management of lupus nephritis was published in January 2024. The guideline made the following practice point: "Rituximab may be considered for patients with



persistent disease activity or inadequate response to initial standard-of-care therapy." In this setting, the treatment algorithm recommended adding rituximab to other biologic therapies.

A KDIGO guideline for the management of ANCA-associated vasculitis (AAV) was published in March 2024. The following recommendations were provided:

- "We recommend that glucocorticoids in combination with rituximab or cyclophosphamide be used as initial treatment of new-onset AAV."
 - Rituximab was noted to be preferred over cyclophosphamide for induction therapy in AAV in the following populations: children and adolescents; premenopausal women and men concerned about fertility; frail older adults; those requiring glucocorticoid sparing; relapsing disease; and PR3-ANCA-associated disease.
- "We recommend maintenance therapy with either rituximab, or azathioprine and low-dose glucocorticoids after induction of remission."
 - Rituximab was noted to be preferred over azathioprine for maintenance therapy in AAV in the following populations: relapsing disease; PR3-ANCA-associated disease; frail older adults; those requiring glucocorticoid sparing; and azathioprine allergy.
- "Patients with relapsing disease should be reinduced, preferably with rituximab."
- "Refractory disease can be treated by an increase in glucocorticoids (intravenous or oral), by the addition of rituximab if cyclophosphamide induction had been used previously, or vice versa."

Myasthenia Gravis Foundation of America

In 2020, a multinational Task Force appointed by the Myasthenia Gravis Foundation of America published updated recommendations for the management of myasthenia gravis. The following recommendations were made regarding the use of rituximab:

- "Rituximab should be considered as an early therapeutic option in patients with muscle-specific kinase antibody-positive (MuSK-Ab+) MG [myasthenia gravis] who have an unsatisfactory response to initial immunotherapy."



- "The efficacy of rituximab in refractory acetylcholine receptor-positive (AChR-Ab+) MG is uncertain. It is an option if patients fail or do not tolerate other immunosuppressive (IS) agents"

Medicare National Coverage

There is no national coverage determination.

Regulatory Status

In 1997, rituximab (Rituxan [Biogen; Genentech]) was initially approved by the US Food and Drug Administration (FDA) for the treatment of relapsed or refractory low-grade, CD20-positive, B-cell non-Hodgkin lymphoma (see [Related Policies](#)). Subsequent indications approved by FDA are summarized in [Table 3](#).

In November 2018, Truxima (rituximab-abbs; Celltrion), July 2019 Ruxience (rituximab-pvvr; Pfizer), and December 2020 Riabni (rituximab-arrx; Amgen) were approved by the FDA as biosimilars of rituximab.

Table 3. FDA-Approved Indications for Rituximab

Date	Indication
1997	<ul style="list-style-type: none"> • Relapsed or refractory low-grade or follicular, CD20-positive, B-cell NHL [modified in 2008 to state, "as a single agent"]
2006	<ul style="list-style-type: none"> • First-line treatment of [modified in 2008 to state, "Previously untreated"] diffuse large B-cell, CD20-positive, NHL in combination with CHOP or other anthracycline-based chemotherapy regimens • In combination with MTX to reduce signs and symptoms in adults with moderately to severely active RA who have had an inadequate response to 1 or more TNF-antagonist therapies • First-line treatment of [modified in 2008 to state, "Previously untreated"] follicular, CD20-positive, B-cell NHL in combination with CVP chemotherapy [modified in 2011 to state, "in combination with first-line chemotherapy] • Treatment of low-grade, CD20-positive, B-cell NHL in patients with stable disease or who achieve a PR or CR following first-line treatment with CVP chemotherapy [modified in 2008 to state, "Treatment of non-progressing (including stable disease), low-grade, CD20-positive, B-cell NHL, as a single agent, after first-line CVP chemotherapy"]
2010	<ul style="list-style-type: none"> • In combination with FC for the treatment of patients with previously untreated and previously treated CD20-positive CLL
2011	<ul style="list-style-type: none"> • Single-agent maintenance therapy for patients with follicular, CD20-positive, B-cell NHL who achieve a CR or PR to first-line rituximab in combination with chemotherapy



Date	Indication
	<ul style="list-style-type: none"> In combination with glucocorticoids for the treatment of adult patients with Wegener granulomatosis and microscopic polyangiitis
2018	<ul style="list-style-type: none"> Treatment of adult patients with moderate to severe pemphigus vulgaris
2019	<ul style="list-style-type: none"> In combination with glucocorticoids for the treatment of adult and pediatric patients 2 years of age and older with patients with Wegener’s granulomatosis and microscopic polyangiitis

CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone; CLL: chronic lymphocytic leukemia; CR: complete response; CVP: cyclophosphamide, vincristine, prednisone; FC: fludarabine, cyclophosphamide; FDA: Food and Drug Administration; MTX: methotrexate; NHL: non-Hodgkin lymphoma; PR: partial response; RA: rheumatoid arthritis; TNF: tumor necrosis factor.

2020 Update

Added Ruxience (rituximab-pvvr) to site-of-service review. Updated coverage criteria for the rituximab products for the treatment of rheumatoid arthritis by adding Rinvoq (upadacitinib) as a first-line treatment option. Updated information on pregnancy as document within the prescribing information and the guidelines from The American Society of Hematology (2019) for the treatment of immune thrombocytopenia (ITP).

2021 Update

Added the biosimilar Riabni (rituximab-arrx) to policy as a second-line agent for the treatment of all covered indications listed in policy. Added links to the ACR, EULAR/ACR, and SLICC criteria. Updated Practice Guidelines and Position Statements and References in policy.

2023 Update

Reviewed prescribing information of all drugs in the policy. Moved Ruxience to second line (non-preferred) products. Changed patient to individual throughout the policy for the process of standardization. Removed trademarks from the brand products throughout the policy for the process of standardization. Added preferred Humira biosimilars (Amjevita with NDC starting with 55513, Cyltezo LCF, Hyrimoz HCF and adamilumab- adaz HCF (Sandoz – unbranded) to the list of preferred products to be tried and failed prior to using preferred Rituxan products as second line therapy for the indication of Rheumatoid Arthritis. Updated Amjevita [NDCs starting with 55513] to a non-preferred product effective January 1, 2024. Added Hyrimoz (Cordavis) [NDCs starting with 83457] as a non-preferred product effective January 1, 2024. Added adalimumab-adbm (Cyltezo unbranded) as a preferred product effective January 1, 2024.



Updated Hyrimoz LCF (Sandoz) from a non-preferred to a preferred product effective January 1, 2024.

2024 Update

Reviewed prescribing information of all drugs in the policy. Clarified that Humira (adalimumab) (AbbVie) [NDCs starting with 00074] is the preferred Humira product for rheumatoid arthritis. Added Simlandi (adalimumab-ryvk) and adalimumab-ryvk (Simlandi unbranded) as preferred products. Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing information. Added the following note to the rheumatoid arthritis criteria regarding the preferred adalimumab product list: This list of preferred adalimumab products does not apply to one Open formulary (Formulary ID: 6062; Rx Plan F1) and one Incentive formulary (Formulary ID: 6064; Rx Plan G3). The preferred adalimumab products for members with these custom Open and Incentive formulary plans are the following: Adalimumab-adaz (Hyrimoz unbranded), adalimumab-adbm (Cyltezo unbranded), adalimumab-ryvk (Simlandi unbranded), Cyltezo (adalimumab-adbm), Humira (adalimumab) (AbbVie) [NDCs starting with 00074], and Simlandi (adalimumab-ryvk). More details can be found in policy 5.01.647 Medical Necessity Criteria for Custom Incentive and Open Formularies. Please check the member Plan booklet or member ID card to determine whether this list of preferred adalimumab products applies. The following changes are effective January 3, 2025. Updated Hyrimoz (Sandoz) (adalimumab-adaz) [NDCs starting with 61314] from a preferred product to a non-preferred product. Changed Ruxience (rituximab-pvvr) to a preferred product. Changed Rituxan (rituximab) and Rituxan Hycela (rituximab and hyaluronidase human) to non-preferred products. Updated coverage criteria for Riabni (rituximab-arrx), Rituxan, and Rituxan Hycela to require the individual has had an adequate trial and failure with Ruxience or Truxima.

2025 Update

Policy updated to indicate that Site of Service Medical Necessity criteria does not apply to Alaska fully-insured members pursuant to [Alaska HB 226](#) (accessed January 3, 2025). Clarified that non-formulary exception review authorizations for all drugs listed in this policy may be approved up to 12 months. Added an exception to the site-of-service requirements for certain individuals receiving treatment for cytokine release syndrome (CRS). Removed Humira



(adalimumab) (AbbVie) [NDCs starting with 00074] as a first-line step therapy option for the rheumatoid arthritis criteria.

References

1. Thaler KJ, Gartlehner G, Kien C, et al. Drug Class Review: Targeted Immune Modulators: Final Update 3 Report. Portland OR: Oregon Health & Science University; 2012.
2. Biogen and Genentech. Rituxan (rituximab) injection for intravenous infusion prescribing information. December, 2021; https://www.gene.com/download/pdf/rituxan_prescribing.pdf Accessed January 6, 2025.
3. Packman CH. Hemolytic anemia due to warm autoantibodies. *Blood Rev.* Jan 2008;22(1):17-31. PMID 17904259
4. Petz LD. Cold antibody autoimmune hemolytic anemias. *Blood Rev.* Jan 2008;22(1):1-15. PMID 17904258
5. Crowther M, Chan YL, Garbett IK, et al. Evidence-based focused review of the treatment of idiopathic warm immune hemolytic anemia in adults. *Blood.* Oct 13 2011;118(15):4036-4040. PMID 21778343
6. Bussone G, Ribeiro E, Dechartres A, et al. Efficacy and safety of rituximab in adults' warm antibody autoimmune haemolytic anemia: retrospective analysis of 27 cases. *Am J Hematol.* Mar 2009;84(3):153-157. PMID 19123460
7. Michel M, Terriou L, Roudot-Thoraval F, et al. A randomized and double-blind controlled trial evaluating the safety and efficacy of rituximab for warm auto-immune hemolytic anemia in adults (the RAIHA study). *Am J Hematol.* Jan 2017;92(1):23-27. PMID 27696475
8. Birgens H, Frederiksen H, Hasselbalch HC, et al. A phase III randomized trial comparing glucocorticoid monotherapy versus glucocorticoid and rituximab in patients with autoimmune haemolytic anaemia. *Br J Haematol.* Nov 2013;163(3):393-399. PMID 23981017
9. Reynaud Q, Durieu I, Dutertre M, et al. Efficacy and safety of rituximab in auto-immune hemolytic anemia: A meta-analysis of 21 studies. *Autoimmun Rev.* Apr 2015;14(4):304-313. PMID 25497766
10. Auger S, Duny Y, Rossi JF, et al. Rituximab before splenectomy in adults with primary idiopathic thrombocytopenic purpura: a meta-analysis. *Br J Haematol.* Aug 2012;158(3):386-398. PMID 22612239
11. Arnold DM, Heddle NM, Carruthers J, et al. A pilot randomized trial of adjuvant rituximab or placebo for nonsplenectomized patients with immune thrombocytopenia. *Blood.* Feb 9 2012;119(6):1356-1362. PMID 22223819
12. Liang Y, Zhang L, Gao J, et al. Rituximab for children with immune thrombocytopenia: a systematic review. *PLoS One.* Jun 2012;7(5):e36698. PMID 22666325
13. Gudbrandsdottir S, Birgens HS, Frederiksen H, et al. Rituximab and dexamethasone vs dexamethasone monotherapy in newly diagnosed patients with primary immune thrombocytopenia. *Blood.* Mar 14 2013;121(11):1976-1981. PMID 23293082
14. Ghanima W, Khelif A, Waage A, et al. Rituximab as second-line treatment for adult immune thrombocytopenia (the RITP trial): a multicentre, randomised, double-blind, placebo-controlled trial. *Lancet.* Apr 25 2015;385(9978):1653-1661. PMID 25662413
15. Tun NM, Villani GM. Efficacy of rituximab in acute refractory or chronic relapsing non-familial idiopathic thrombotic thrombocytopenic purpura: a systematic review with pooled data analysis. *J Thromb Thrombolysis.* Oct 2012;34(3):347-359. PMID 22547089
16. Froissart A, Buffet M, Veyradier A, et al. Efficacy and safety of first-line rituximab in severe, acquired thrombotic thrombocytopenic purpura with a suboptimal response to plasma exchange. Experience of the French Thrombotic Microangiopathies Reference Center. *Crit Care Med.* Jan 2012;40(1):104-111. PMID 21926591



17. Scully M, Hunt BJ, Benjamin S, et al. Guidelines on the diagnosis and management of thrombotic thrombocytopenic purpura and other thrombotic microangiopathies. *Br J Haematol*. Aug 2012;158(3):323-335. PMID 22624596
18. Harambat J, Lamireau D, Delmas Y, et al. Successful treatment with rituximab for acute refractory thrombotic thrombocytopenic purpura related to acquired ADAMTS13 deficiency: a pediatric report and literature review. *Pediatr Crit Care Med*. Mar 2011;12(2):e90-93. PMID 20625343
19. Scully M, McDonald V, Cavenagh J, et al. A phase 2 study of the safety and efficacy of rituximab with plasma exchange in acute acquired thrombotic thrombocytopenic purpura. *Blood*. Aug 18 2011;118(7):1746-1753. PMID 21636861
20. Scully M, Cohen H, Cavenagh J, et al. Remission in acute refractory and relapsing thrombotic thrombocytopenic purpura following rituximab is associated with a reduction in IgG antibodies to ADAMTS-13. *Br J Haematol*. Feb 2007;136(3):451-461. PMID 17233847
21. Mahr A, Moosig F, Neumann T, et al. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss): evolutions in classification, etiopathogenesis, assessment and management. *Curr Opin Rheumatol*. Jan 2014;26(1):16-23. PMID 24257370
22. Clain JM, Cartin-Ceba R, Fervenza FC, et al. Experience with rituximab in the treatment of antineutrophil cytoplasmic antibody associated vasculitis. *Ther Adv Musculoskelet Dis*. Apr 2014;6(2):58-74. PMID 24688606
23. Thiel J, Troilo A, Salzer U, et al. Rituximab as induction therapy in eosinophilic granulomatosis with polyangiitis refractory to conventional immunosuppressive treatment: a 36-month follow-up analysis. *J Allergy Clin Immunol Pract*. Nov - Dec 2017;5(6):1556-1563. PMID 28916432
24. Novikov P, Moiseev S, Smitienko I, et al. Rituximab as induction therapy in relapsing eosinophilic granulomatosis with polyangiitis: A report of 6 cases. *Joint Bone Spine*. Jan 2016;83(1):81-84. PMID 26494587
25. Mohammad AJ, Hot A, Arndt F, et al. Rituximab for the treatment of eosinophilic granulomatosis with polyangiitis (Churg-Strauss). *Ann Rheum Dis*. Feb 2016;75(2):396-401. PMID 25467294
26. Muñoz SA, Gandino IJ, Orden AO, et al. Rituximab in the treatment of eosinophilic granulomatosis with polyangiitis. *Reumatol Clin*. May-Jun 2015;11(3):165-169. PMID 25523986
27. Thiel J, Hassler F, Salzer U, et al. Rituximab in the treatment of refractory or relapsing eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome). *Arthritis Res Ther*. Nov 2013;15(5):R133. PMID 24286362
28. National Heart Lung and Blood Institute. Hemophilia. n.d.; <https://www.nhlbi.nih.gov/health-topics/hemophilia> Accessed January 6, 2025.
29. Huth-Kuhne A, Baudo F, Collins P, et al. International recommendations on the diagnosis and treatment of patients with acquired hemophilia A. *Haematologica*. Apr 2009;94(4):566-575. PMID 19336751
30. Collins PW, Chalmers E, Hart DP, et al. Diagnosis and treatment of factor VIII and IX inhibitors in congenital haemophilia: (4th edition). UK Haemophilia Centre Doctors Organization. *Br J Haematol*. Jan 2013;160(2):153-170. PMID 23157203
31. Laros-van Gorkom BA, Falaise C, Astermark J. Immunosuppressive agents in the treatment of inhibitors in congenital haemophilia A and B--a systematic literature review. *Eur J Haematol Suppl*. Aug 2014;76:26-38. PMID 24957105
32. Franchini M, Mengoli C, Lippi G, et al. Immune tolerance with rituximab in congenital haemophilia with inhibitors: a systematic literature review based on individual patients' analysis. *Haemophilia*. Sep 2008;14(5):903-912. PMID 18671801
33. Leissinger C, Josephson CD, Granger S, et al. Rituximab for treatment of inhibitors in haemophilia A. A Phase II study. *Thromb Haemost*. Sep 2 2014;112(3):445-458. PMID 24919980
34. Deodhar A. Update in rheumatology: evidence published in 2012. *Ann Intern Med*. Jun 18 2013;158(12):903-906. PMID 23580081
35. Dammacco F, Sansonno D. Therapy for hepatitis C virus-related cryoglobulinemic vasculitis. *N Engl J Med*. Sep 12 2013;369(11):1035-1045. PMID 24024840
36. Puéchal X, Guillevin L. Therapeutic immunomodulation in systemic vasculitis: taking stock. *Joint Bone Spine*. Jul 2013;80(4):374-379. PMID 23237994



37. Pietrogrande M, De Vita S, Zignego AL, et al. Recommendations for the management of mixed cryoglobulinemia syndrome in hepatitis C virus-infected patients. *Autoimmun Rev.* Jun 2011;10(8):444-454. PMID 21303705
38. Sneller MC, Hu Z, Langford CA. A randomized controlled trial of rituximab following failure of antiviral therapy for hepatitis C virus-associated cryoglobulinemic vasculitis. *Arthritis Rheum.* Mar 2012;64(3):835-842. PMID 22147444
39. De Vita S, Quartuccio L, Isola M, et al. A randomized controlled trial of rituximab for the treatment of severe cryoglobulinemic vasculitis. *Arthritis Rheum.* Mar 2012;64(3):843-853. PMID 22147661
40. Visentini M, Tinelli C, Colantuono S, et al. Efficacy of low-dose rituximab for the treatment of mixed cryoglobulinemia vasculitis: Phase II clinical trial and systematic review. *Autoimmun Rev.* Oct 2015;14(10):889-896. PMID 26031898
41. Ortega-Hernandez OD, Shoenfeld Y. Mixed connective tissue disease: an overview of clinical manifestations, diagnosis and treatment. *Best Pract Res Clin Rheumatol.* Feb 2012;26(1):61-72. PMID 22424193
42. Lepri G, Avouac J, Airo P, et al. Effects of rituximab in connective tissue disorders related interstitial lung disease. *Clin Exp Rheumatol.* Sep-Oct 2016;34(5 Suppl 100):181-185. PMID 27749242
43. Jansson AF, Sengler C, Kuemmerle-Deschner J, et al. B cell depletion for autoimmune diseases in paediatric patients. *Clin Rheumatol.* Jan 2011;30(1):87-97. PMID 21120559
44. Mylona EE, Barabotis IG, Lekakis LJ, et al. Multicentric Castleman's disease in HIV infection: a systematic review of the literature. *AIDS Rev.* Jan-Mar 2008;10(1):25-35. PMID 18385778
45. Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. 2023; **HIV Clinical Guidelines: Adult and Adolescent Opportunistic Infections - What's New in the Guidelines | Clinicalinfo.HIV.gov** Accessed January 6, 2025.
46. Reid E, Nooka A, Blackmon J, et al. Clinical use of rituximab in patients with HIV related lymphoma and Multicentric Castleman's disease. *Curr Drug Deliv.* Jan 2012;9(1):41-51. PMID 22023215
47. Gerard L, Michot JM, Burcheri S, et al. Rituximab decreases the risk of lymphoma in patients with HIV-associated multicentric Castleman disease. *Blood.* Mar 8 2012;119(10):2228-2233. PMID 22223822
48. Hoffmann C, Schmid H, Muller M, et al. Improved outcome with rituximab in patients with HIV-associated multicentric Castleman disease. *Blood.* Sep 29 2011;118(13):3499-3503. PMID 21778341
49. Shin D-y, Jeon YK, Hong Y-s, et al. Clinical dissection of multicentric Castleman disease. *Leuk Lymphoma.* 2011;52(8):1517-1522. PMID 21585280
50. Souza FB, Porfirio GJ, Andriolo BN, et al. Rituximab effectiveness and safety for treating primary Sjogren's syndrome (PPS): systematic review and meta-analysis. *PLoS One.* 2016;11(3):e0150749. PMID 26998607
51. Ramos-Casals M, Tzioufas AG, Stone JH, et al. Treatment of primary Sjogren syndrome: a systematic review. *JAMA.* Jul 28 2010;304(4):452-460. PMID 20664046
52. Devauchelle-Pensec V, Mariette X, Jousse-Joulin S, et al. Treatment of primary Sjogren syndrome with rituximab: a randomized trial. *Ann Intern Med.* Feb 18 2014;160(4):233-242. PMID 24727841
53. Carubbi F, Cipriani P, Marrelli A, et al. Efficacy and safety of rituximab treatment in early primary Sjogren's syndrome: a prospective, multi-center, follow-up study. *Arthritis Res Ther.* Nov 2013;15(5):R172. PMID 24286296
54. Gottenberg JE, Cinquetti G, Larroche C, et al. Efficacy of rituximab in systemic manifestations of primary Sjogren's syndrome: results in 78 patients of the AutoImmune and Rituximab registry. *Ann Rheum Dis.* Jun 2013;72(6):1026-1031. PMID 23264337
55. Mekinian A, Ravaud P, Larroche C, et al. Rituximab in central nervous system manifestations of patients with primary Sjogren's syndrome: results from the AIR registry. *Clin Exp Rheumatol.* Mar-Apr 2012;30(2):208-212. PMID 22341206
56. Mekinian A, Ravaud P, Hatron PY, et al. Efficacy of rituximab in primary Sjogren's syndrome with peripheral nervous system involvement: results from the AIR registry. *Ann Rheum Dis.* Jan 2012;71(1):84-87. PMID 21926185



57. Borba HH, Wiens A, de Souza TT, et al. Efficacy and safety of biologic therapies for systemic lupus erythematosus treatment: systematic review and meta-analysis. *BioDrugs*. Apr 2014;28(2):211-228. PMID 24190520
58. Duxbury B, Combescure C, Chizzolini C. Rituximab in systemic lupus erythematosus: an updated systematic review and meta-analysis. *Lupus*. Dec 2013;22(14):1489-1503. PMID 24135078
59. Cobo-Ibanez T, Loza-Santamaria E, Pego-Reigosa JM, et al. Efficacy and safety of rituximab in the treatment of non-renal systemic lupus erythematosus: a systematic review. *Semin Arthritis Rheum*. Oct 2014;44(2):175-185. PMID 24830791
60. Lan L, Han F, Chen JH. Efficacy and safety of rituximab therapy for systemic lupus erythematosus: a systematic review and meta-analysis. *J Zhejiang Univ Sci B*. Sep 2012;13(9):731-744. PMID 22949364
61. Andrade-Ortega L, Irazoque-Palazuelos F, Lopez-Villanueva R, et al. [Efficacy of rituximab versus cyclophosphamide in lupus patients with severe manifestations. A randomized and multicenter study] [Spanish]. *Reumatol Clin*. Sep-Oct 2010;6(5):250-255. PMID 21794725
62. Merrill JT, Neuwelt CM, Wallace DJ, et al. Efficacy and safety of rituximab in moderately-to-severely active systemic lupus erythematosus: the randomized, double-blind, phase II/III systemic lupus erythematosus evaluation of rituximab trial. *Arthritis Rheum*. Jan 2010;62(1):222-233. PMID 20039413
63. Merrill J, Buyon J, Furie R, et al. Assessment of flares in lupus patients enrolled in a phase II/III study of rituximab (EXPLORER). *Lupus*. Jun 2011;20(7):709-716. PMID 21478286
64. Rudnicka L, Olszewska M, Kardynal A. Unanswered questions in evaluating rituximab efficacy: comment on the article by Merrill et al [letter]. *Arthritis Rheum*. Aug 2010;62(8):2566. PMID 20496370
65. Rovin BH, Furie R, Latinis K, et al. Efficacy and safety of rituximab in patients with active proliferative lupus nephritis: the Lupus Nephritis Assessment with Rituximab study. *Arthritis Rheum*. Apr 2012;64(4):1215-1226. PMID 22231479
66. Lightstone L. The landscape after LUNAR: rituximab's crater-filled path [editorial]. *Arthritis Rheum*. Apr 2012;64(4):962-965. PMID 22231618
67. Henderson LK, Masson P, Craig JC, et al. Induction and maintenance treatment of proliferative lupus nephritis: a meta-analysis of randomized controlled trials. *Am J Kidney Dis*. Jan 2013;61(1):74-87. PMID 23182601
68. Goswami RP, Sircar G, Sit H et al. Cyclophosphamide Versus Mycophenolate Versus Rituximab in Lupus Nephritis Remission Induction: A Historical Head-to-Head Comparative Study. *J Clin Rheumatol*, 2018 Mar 22;25(1). PMID 29561474.
69. Weidenbusch M, Rommele C, Schrottler A, et al. Beyond the LUNAR trial. Efficacy of rituximab in refractory lupus nephritis. *Nephrol Dial Transplant*. Jan 2013;28(1):106-111. PMID 22764193
70. Diaz-Lagares C, Croca S, Sangle S, et al. Efficacy of rituximab in 164 patients with biopsy-proven lupus nephritis: pooled data from European cohorts. *Autoimmun Rev*. Mar 2012;11(5):357-364. PMID 22032879
71. Phumethum V, Jamal S, Johnson SR. Biologic therapy for systemic sclerosis: a systematic review. *J Rheumatol*. Feb 2011;38(2):289-296. PMID 21041277
72. Daoussis D, Liossis SN, Tsamandas AC, et al. Experience with rituximab in scleroderma: results from a 1-year, proof-of-principle study. *Rheumatology (Oxford)*. Feb 2010;49(2):271-280. PMID 19447770
73. McQueen FM, Solanki K. Rituximab in diffuse cutaneous systemic sclerosis: should we be using it today? *Rheumatology (Oxford)*. May 2015;54(5):757-767. PMID 25573841
74. Elhai M, Boubaya M, Distler O et al. Outcomes of patients with systemic sclerosis treated with rituximab in contemporary practice: a prospective cohort study. *Ann. Rheum. Dis.*, 2019 Apr 11;78(7). PMID 30967395.
75. Jordan S, Distler JH, Maurer B, et al. Effects and safety of rituximab in systemic sclerosis: an analysis from the European Scleroderma Trial and Research (EUSTAR) group. *Ann Rheum Dis*. Jun 2015;74(6):1188-1194. PMID 24442885
76. Khanna D, Furst DE, Hays RD, et al. Minimally important difference in diffuse systemic sclerosis: results from the D-penicillamine study. *Ann Rheum Dis*. Oct 2006;65(10):1325-1329. PMID 16540546



77. Sumida H, Asano Y, Tamaki Z, et al. Successful experience of rituximab therapy for systemic sclerosis-associated interstitial lung disease with concomitant systemic lupus erythematosus. *J Dermatol*. May 2014;41(5):418-420. PMID 24801917
78. Moazedi-Fuerst FC, Kielhauser SM, Brickmann K, et al. Rituximab for systemic sclerosis: arrest of pulmonary disease progression in five cases. Results of a lower dosage and shorter interval regimen. *Scand J Rheumatol*. 2014;43(3):257-258. PMID 24611681
79. Braun-Moscovici Y, Butbul-Aviel Y, Guralnik L, et al. Rituximab: rescue therapy in life-threatening complications or refractory autoimmune diseases: a single center experience. *Rheumatol Int*. Jun 2013;33(6):1495-1504. PMID 23239037
80. Daoussis D, Liossis SN, Tsamandas AC, et al. Effect of long-term treatment with rituximab on pulmonary function and skin fibrosis in patients with diffuse systemic sclerosis. *Clin Exp Rheumatol*. Mar-Apr 2012;30(2 Suppl 71):S17-22. PMID 22244622
81. Khor CG, Chen XL, Lin TS, et al. Rituximab for refractory digital infarcts and ulcers in systemic sclerosis. *Clin Rheumatol*. Jul 2014;33(7):1019-1020. PMID 24722688
82. Smith V, Piette Y, van Praet JT, et al. Two-year results of an open pilot study of a 2-treatment course with rituximab in patients with early systemic sclerosis with diffuse skin involvement. *J Rheumatol*. Jan 2013;40(1):52-57. PMID 23118116
83. Chartrand S, Swigris JJ, Peykova L, et al. Rituximab for the treatment of connective tissue disease-associated interstitial lung disease. *Sarcoidosis Vasc Diffuse Lung Dis*. Feb 2015;32(4):296-304. PMID 26847096
84. He D, Guo R, Zhang F, et al. Rituximab for relapsing-remitting multiple sclerosis. *Cochrane Database Syst Rev*. Dec 6 2013;12(12):CD009130. PMID 24310855
85. Hauser SL, Waubant E, Arnold DL, et al. B-cell depletion with rituximab in relapsing-remitting multiple sclerosis. *N Engl J Med*. Feb 14 2008;358(7):676-688. PMID 18272891
86. Daumer M, Neuhaus A, Morrissey S, et al. MRI as an outcome in multiple sclerosis clinical trials. *Neurology*. Feb 24 2009;72(8):705-711. PMID 19073945
87. Goodin DS, Traboulsee A, Knappertz V, et al. Relationship between early clinical characteristics and long term disability outcomes: 16 year cohort study (follow-up) of the pivotal interferon beta-1b trial in multiple sclerosis. *J Neurol Neurosurg Psychiatry*. Mar 2012;83(3):282-287. PMID 22193561
88. Castillo-Trivino T, Braithwaite D, Bacchetti P, et al. Rituximab in relapsing and progressive forms of multiple sclerosis: a systematic review. *PLoS One*. Jul 2013;8(7): e66308. PMID 23843952
89. Hawker K, O'Connor P, Freedman MS, et al. Rituximab in patients with primary progressive multiple sclerosis: results of a randomized double-blind placebo-controlled multicenter trial. *Ann Neurol*. Oct 2009;66(4):460-471. PMID 19847908
90. Bar-Or A, Calabresi PA, Arnold D, et al. Rituximab in relapsing-remitting multiple sclerosis: a 72-week, open-label, phase I trial. *Ann Neurol*. Mar 2008;63(3):395-400. PMID 18383069
91. Naismith RT, Piccio L, Lyons JA, et al. Rituximab add-on therapy for breakthrough relapsing multiple sclerosis: a 52-week phase II trial. *Neurology*. Jun 8 2010;74(23):1860-1867. PMID 20530322
92. Scotti B, Disanto G, Sacco R et al. Effectiveness and safety of Rituximab in multiple sclerosis: an observational study from Southern Switzerland. *PLoS ONE*, 2018 May 15;13(5). PMID 29758075.
93. Hu Y, Nie H, Yu HH et al. Efficacy and safety of rituximab for relapsing-remitting multiple sclerosis: A systematic review and meta-analysis. *Autoimmun Rev*, 2019 Mar 8;18(5). PMID 30844555.
94. Alcalá C, Gascón F, Pérez-Mirallas F et al. Treatment with alemtuzumab or rituximab after fingolimod withdrawal in relapsing-remitting multiple sclerosis is effective and safe. *J. Neurol.*, 2019 Jan 21;266(3). PMID 30661133.
95. Yamout BI, El-Ayoubi NK, Nicolas J et al. Safety and Efficacy of Rituximab in Multiple Sclerosis: A Retrospective Observational Study. *J Immunol Res*, 2018 Dec 13;2018:9084759. PMID 30539030.
96. Salzer J, Svenningsson R, Alping P, et al. Rituximab in multiple sclerosis: A retrospective observational study on safety and efficacy. *Neurology*. Nov 15 2016;87(20):2074-2081. PMID 27760868
97. Waubant E, Cross A. MS and related disorders: groundbreaking news. *Lancet Neurol*. Jan 2014;13(1):11-13. PMID 24331785



98. Jarius S, Wildemann B. Aquaporin-4 antibodies (NMO-IgG) as a serological marker of neuromyelitis optica: a critical review of the literature. *Brain Pathol.* Nov 2013;23(6):661-683. PMID 24118483
99. Frohman EM, Wingerchuk DM. Clinical practice. Transverse myelitis. *N Engl J Med.* Aug 5 2010;363(6):564-572. PMID 20818891
100. Wingerchuk DM, Lennon VA, Pittock SJ, et al. Revised diagnostic criteria for neuromyelitis optica. *Neurology.* May 23 2006;66(10):1485-1489. PMID 16717206
101. Scott TF, Frohman EM, De Seze J, et al. Evidence-based guideline: clinical evaluation and treatment of transverse myelitis: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology.* Dec 13 2011;77(24):2128-2134. PMID 22156988
102. Trebst C, Jarius S, Berthele A, et al. Update on the diagnosis and treatment of neuromyelitis optica: recommendations of the Neuromyelitis Optica Study Group (NEMOS). *J Neurol.* Jan 2014;261(1):1-16. PMID 24272588
103. Gao F, Chai B, Gu C et al. Effectiveness of rituximab in neuromyelitis optica: a meta-analysis. *BMC Neurol.* 2019 Mar 8;19(1). PMID 30841862.
104. Kim SH, Kim W, Li XF, et al. Repeated treatment with rituximab based on the assessment of peripheral circulating memory B cells in patients with relapsing neuromyelitis optica over 2 years. *Arch Neurol.* Nov 2011;68(11):1412-1420. PMID 21747007
105. Damato V, Evoli A, Iorio R. Efficacy and safety of rituximab therapy in neuromyelitis optica spectrum disorders: a systematic review and meta-analysis. *JAMA Neurol.* Nov 01 2016;73(11):1342-1348. PMID 27668357
106. Radaelli M, Moiola L, Sangalli F, et al. Neuromyelitis optica spectrum disorders: long-term safety and efficacy of rituximab in Caucasian patients. *Mult Scler.* Apr 2016;22(4):511-519. PMID 26199350
107. Nikoo Z, Badihian S, Shaygannejad V et al. Comparison of the efficacy of azathioprine and rituximab in neuromyelitis optica spectrum disorder: a randomized clinical trial. *J. Neurol.,* 2017 Aug 24;264(9). PMID 28831548.
108. Torres J, Pruitt A, Balcer L, et al. Analysis of the treatment of neuromyelitis optica. *J Neurol Sci.* Apr 15 2015;351(1-2):31-35. PMID 25727350
109. Mealy MA, Wingerchuk DM, Palace J, et al. Comparison of relapse and treatment failure rates among patients with neuromyelitis optica: multicenter study of treatment efficacy. *JAMA Neurol.* Mar 2014;71(3):324-330. PMID 24445513
110. Tandan R, Hehir MK, 2nd, Waheed W, et al. Rituximab treatment of myasthenia gravis: A systematic review. *Muscle Nerve.* Aug 2017;56(2):185-196. PMID 28164324
111. Hehir MK, Hobson-Webb LD, Benatar M, et al. Rituximab as treatment for anti-MuSK myasthenia gravis: Multicenter blinded prospective review. *Neurology.* Sep 05 2017;89(10):1069-1077. PMID 28801338
112. Dahan K, Debiec H, Plaisier E, et al. Rituximab for severe membranous nephropathy: a 6-month trial with extended follow-up. *J Am Soc Nephrol.* Jan 2017;28(1):348-358. PMID 27352623
113. Fervenza FC, Appel GB, Barbour SJ et al. Rituximab or Cyclosporine in the Treatment of Membranous Nephropathy. *N. Engl. J. Med.,* 2019 Jul 4;381(1). PMID 31269364.
114. Ruggenti P, Cravedi P, Chianca A, et al. Rituximab in idiopathic membranous nephropathy. *J Am Soc Nephrol.* Aug 2012;23(8):1416-1425. PMID 22822077
115. Fervenza FC, Abraham RS, Erickson SB, et al. Rituximab therapy in idiopathic membranous nephropathy: a 2-year study. *Clin J Am Soc Nephrol.* Dec 2010;5(12):2188-2198. PMID 20705965
116. Moroni G, Depetri F, Del Vecchio L, et al. Low-dose rituximab is poorly effective in patients with primary membranous nephropathy. *Nephrol Dial Transplant.* Oct 01 2017;32(10):1691-1696. PMID 27387472
117. Munyentwali H, Bouachi K, Audard V, et al. Rituximab is an efficient and safe treatment in adults with steroid-dependent minimal change disease. *Kidney Int.* Mar 2013;83(3):511-516. PMID 23325085
118. Hoxha E, Stahl RA, Harendza S. Rituximab in adult patients with immunosuppressive-dependent minimal change disease. *Clin Nephrol.* Aug 2011;76(2):151-158. PMID 21762648



119. Sinha A, Bagga A. Rituximab therapy in nephrotic syndrome: implications for patients' management. *Nat Rev Nephrol.* Mar 2013;9(3):154-169. PMID 23338210
120. Iwabuchi Y, Takei T, Moriyama T, et al. Long-term prognosis of adult patients with steroid-dependent minimal change nephrotic syndrome following rituximab treatment. *Medicine (Baltimore).* Dec 2014;93(29):e300. PMID 25546674
121. King C, Logan S, Smith SW, et al. The efficacy of rituximab in adult frequently relapsing minimal change disease. *Clin Kidney J.* Feb 2017;10(1):16-19. PMID 28638601
122. Papakrivopoulou E, Shendi AM, Salama AD, et al. Effective treatment with rituximab for the maintenance of remission in frequently relapsing minimal change disease. *Nephrology (Carlton).* Oct 2016;21(10):893-900. PMID 26860320
123. Jellouli M, Charfi R, Maalej B et al. Rituximab in The Management of Pediatric Steroid-Resistant Nephrotic Syndrome: A Systematic Review. *J. Pediatr.*, 2018 Apr 24;197:191-197.e1. PMID 29680473.
124. Ravani P, Rossi R, Bonanni A, et al. Rituximab in children with steroid-dependent nephrotic syndrome: a multicenter, open-label, noninferiority, randomized controlled trial. *J Am Soc Nephrol.* Sep 2015;26(9):2259-2266. PMID 25592855
125. Iijima K, Sako M, Nozu K, et al. Rituximab for childhood-onset, complicated, frequently relapsing nephrotic syndrome or steroid-dependent nephrotic syndrome: a multicentre, double-blind, randomised, placebo-controlled trial. *Lancet.* Oct 4 2014;384(9950):1273-1281. PMID 24965823
126. Boumediene A, Vachin P, Sendeyo K et al. NEPHRUTIX: A randomized, double-blind, placebo vs Rituximab-controlled trial assessing T-cell subset changes in Minimal Change Nephrotic Syndrome. *J. Autoimmun.*, 2017 Oct 24;88:91-102. PMID 29056249.
127. Hoseini R, Sabzian K, Otukesh H et al. Efficacy and Safety of Rituximab in Children With Steroid- and Cyclosporine-resistant and Steroid- and Cyclosporine-dependent Nephrotic Syndrome. *Iran J Kidney Dis*, 2018 Feb 9;12(1). PMID 29421774.
128. Dignan FL, Amrolia P, Clark A, et al. Diagnosis and management of chronic graft-versus-host disease. *Br J Haematol.* Jul 2012;158(1):46-61. PMID 22533811
129. Wolff D, Schleuning M, von Harsdorf S, et al. Consensus conference on clinical practice in chronic GVHD: second-line treatment of chronic graft-versus-host disease. *Biol Blood Marrow Transplant.* Jan 2011;17(1):1-17. PMID 20685255
130. Kharfan-Dabaja MA, Mhaskar AR, Djulbegovic B, et al. Efficacy of rituximab in the setting of steroid-refractory chronic graft-versus-host disease: a systematic review and meta-analysis. *Biol Blood Marrow Transplant.* Sep 2009;15(9):1005-1013. PMID 19660713
131. Cutler C, Kim HT, Bindra B, et al. Rituximab prophylaxis prevents corticosteroid-requiring chronic GVHD after allogeneic peripheral blood stem cell transplantation: results of a phase 2 trial. *Blood.* Aug 22 2013;122(8):1510-1517. PMID 23861248
132. Arai S, Sahaf B, Narasimhan B, et al. Prophylactic rituximab after allogeneic transplantation decreases B-cell alloimmunity with low chronic GVHD incidence. *Blood.* Jun 21 2012;119(25):6145-6154. PMID 22563089
133. Kim SJ, Lee JW, Jung CW, et al. Weekly rituximab followed by monthly rituximab treatment for steroid-refractory chronic graft-versus-host disease: results from a prospective, multicenter, phase II study. *Haematologica.* Nov 2010;95(11):1935-1942. PMID 20663943
134. Pavletic SZ, Martin P, Lee SJ, et al. Measuring therapeutic response in chronic graft-versus-host disease: National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: IV. Response Criteria Working Group report. *Biol Blood Marrow Transplant.* Mar 2006;12(3):252-266. PMID 16503494
135. Vo AA, Choi J, Cisneros K, et al. Benefits of rituximab combined with intravenous immunoglobulin for desensitization in kidney transplant recipients. *Transplantation.* Aug 15 2014;98(3):312-319. PMID 24770617
136. Zhao YG, Shi BY, Qian YY, et al. Clinical efficacy of rituximab for acute rejection in kidney transplantation: a meta-analysis. *Int Urol Nephrol.* Jun 2014;46(6):1225-1230. PMID 24242738
137. Vo AA, Lukovsky M, Toyoda M, et al. Rituximab and intravenous immune globulin for desensitization during renal transplantation. *N Engl J Med.* Jul 17 2008;359(3):242-251. PMID 18635429



138. Vo AA, Peng A, Toyoda M, et al. Use of intravenous immune globulin and rituximab for desensitization of highly HLA-sensitized patients awaiting kidney transplantation. *Transplantation*. May 15 2010;89(9):1095-1102. PMID 20110854
139. Vo AA, Petrozzino J, Yeung K, et al. Efficacy, outcomes, and cost-effectiveness of desensitization using IVIG and rituximab. *Transplantation*. Mar 27 2013;95(6):852-858. PMID 23511212
140. Barbosa D, Kahwaji J, Puliyaanda D, et al. Polyomavirus BK viremia in kidney transplant recipients after desensitization with IVIG and rituximab. *Transplantation*. Apr 15 2014;97(7):755-761. PMID 24686425
141. Jordan SC, Reinsmoen N, Lai CH, et al. Novel immunotherapeutic approaches to improve rates and outcomes of transplantation in sensitized renal allograft recipients. *Discov Med*. Mar 2012;13(70):235-245. PMID 22463800
142. Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group. KDIGO clinical practice guideline for the care of kidney transplant recipients. *Am J Transplant*. 2009;9(Suppl 3):S1-S157.
143. van den Hoogen MW, Kamburova EG, Baas MC, et al. Rituximab as induction therapy after renal transplantation: a randomized, double-blind, placebo-controlled study of efficacy and safety. *Am J Transplant*. Feb 2015;15(2):407-416. PMID 25612493
144. Tyden G, Genberg H, Tollemar J, et al. A randomized, double-blind, placebo-controlled, study of single-dose rituximab as induction in renal transplantation. *Transplantation*. May 15 2009;87(9):1325-1329. PMID 19424032
145. Costanzo MR, Dipchand A, Starling R, et al. The International Society of Heart and Lung Transplantation Guidelines for the care of heart transplant recipients. *J Heart Lung Transplant*. Aug 2010;29(8):914-956. PMID 20643330
146. Kobashigawa J, Mehra M, West L, et al. Report from a consensus conference on the sensitized patient awaiting heart transplantation. *J Heart Lung Transplant*. Mar 2009;28(3):213-225. PMID 19285611
147. Roberts DM, Jiang SH, Chadban SJ. The treatment of acute antibody-mediated rejection in kidney transplant recipients-a systematic review. *Transplantation*. Oct 27 2012;94(8):775-783. PMID 23032865
148. Sautenet B, Blanco G, Buchler M, et al. One-year results of the effects of rituximab on acute antibody-mediated rejection in renal transplantation: RITUX ERAH, a multicenter double-blind randomized placebo-controlled trial. *Transplantation*. Feb 2016;100(2):391-399. PMID 26555944
149. Zarkhin V, Li L, Kambham N, et al. A randomized, prospective trial of rituximab for acute rejection in pediatric renal transplantation. *Am J Transplant*. Dec 2008;8(12):2607-2617. PMID 18808404
150. Ravichandran AK, Schilling JD, Novak E, et al. Rituximab is associated with improved survival in cardiac allograft patients with antibody-mediated rejection: a single center review. *Clin Transplant*. Nov-Dec 2013;27(6):961-967. PMID 24304378
151. Lanzoni G, Oikawa T, Wang Y, et al. Concise review: clinical programs of stem cell therapies for liver and pancreas. *Stem Cells*. Oct 2013;31(10):2047-2060. PMID 23873634
152. Drachenberg CB, Odorico J, Demetris AJ, et al. Banff schema for grading pancreas allograft rejection: working proposal by a multi-disciplinary international consensus panel. *Am J Transplant*. Jun 2008;8(6):1237-1249. PMID 18444939
153. Barton FB, Rickels MR, Alejandro R, et al. Improvement in outcomes of clinical islet transplantation: 1999-2010. *Diabetes Care*. Jul 2012;35(7):1436-1445. PMID 22723582
154. Torrealba JR, Samaniego M, Pascual J, et al. C4d-positive interacinar capillaries correlates with donor-specific antibody-mediated rejection in pancreas allografts. *Transplantation*. Dec 27 2008;86(12):1849-1856. PMID 19104433
155. Vendrame F, Pileggi A, Laughlin E, et al. Recurrence of type 1 diabetes after simultaneous pancreas-kidney transplantation, despite immunosuppression, is associated with autoantibodies and pathogenic autoreactive CD4 T-cells. *Diabetes*. Apr 2010;59(4):947-957. PMID 20086230
156. Melcher ML, Olson JL, Baxter-Lowe LA, et al. Antibody-mediated rejection of a pancreas allograft. *Am J Transplant*. Feb 2006;6(2):423-428. PMID 16426331
157. Hahn BH, McMahon MA, Wilkinson A, et al. American College of Rheumatology guidelines for screening, treatment, and management of lupus nephritis. *Arthritis Care Res (Hoboken)*. Jun 2012;64(6):797-808. PMID 22556106



158. Neunert C, Lim W, Crowther M, et al. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. *Blood*. Apr 21 2011; 117(16): 4190-207. PMID 21325604
159. Neunert C, Terrell D, Arnold D, et al. The American Society of Hematology 2019 evidence-based practice guideline for immune thrombocytopenia. *Blood Advances*. Oct 21 2019;3829-3866.
160. National Institute for Health and Care Excellence (NICE). Multiple sclerosis in adults: management [CG186]. 2014; <https://www.nice.org.uk/guidance/cg186> Accessed January 6, 2025.
161. Rae-Grant A, Day GS, Marrie RA, et al. Practice guideline recommendations summary: Disease-modifying therapies for adults with multiple sclerosis: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology*. Apr 24 2018;90(17):777-788. PMID 29686116
162. Kobashigawa J, Colvin M, Potena L, et al. The management of antibodies in heart transplantation: An ISHLT consensus document. *J Heart Lung Transplant*. May 2018; 37(5): 537-547. PMID 29452978
163. Singh JA, Saag KG, Bridges SL, Jr., et al. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. *Arthritis Rheumatol*. Jan 2016;68(1):1-26. PMID 26545940
164. National Institute for Health and Care Excellence (NICE). Rituximab in combination with glucocorticoids for treating anti-neutrophil cytoplasmic antibody-associated vasculitis [TA308]. 2014; <https://www.nice.org.uk/guidance/TA308> Accessed January 6, 2025.
165. National Multiple Sclerosis Society. Treating MS: medications. <http://www.nationalmssociety.org/Treating-MS/Medications> Accessed January 6, 2025.
166. Truxima (rituximab-abbs). Prescribing Information. North Wales, PA. Teva Pharmaceuticals USA, Inc. February 2022.
167. Ruxience (rituximab-pvvr). Prescribing Information. New York, NY. Pfizer Labs. October 2023.
168. Riabni (rituximab-arrx). Prescribing Information. Thousand Oaks, CA. Amgen, Inc. February 2023.
169. Lee AS, Scofield RH, Hammitt KM, et al. Consensus Guidelines for Evaluation and Management of Pulmonary Disease in Sjögren's. *Chest*. Feb 2021; 159(2): 683-698. PMID 33075377
170. Johnson SR, Bernstein EJ, Bolster MB, et al. 2023 American College of Rheumatology (ACR)/American College of Chest Physicians (CHEST) Guideline for the Treatment of Interstitial Lung Disease in People with Systemic Autoimmune Rheumatic Diseases. *Arthritis Rheumatol*. Aug 2024; 76(8): 1182-1200. PMID 38978310
171. Chung SA, Langford CA, Maz M, et al. 2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Antineutrophil Cytoplasmic Antibody-Associated Vasculitis. *Arthritis Rheumatol*. Aug 2021; 73(8): 1366-1383. PMID 34235894
172. Raghu G, Montesi SB, Silver RM, et al. Treatment of Systemic Sclerosis-associated Interstitial Lung Disease: Evidence-based Recommendations. An Official American Thoracic Society Clinical Practice Guideline. *Am J Respir Crit Care Med*. Jan 15 2024; 209(2): 137-152. PMID 37772985
173. Costanzo MR, Dipchand A, Starling R, et al. The International Society of Heart and Lung Transplantation Guidelines for the care of heart transplant recipients. *J Heart Lung Transplant*. Aug 2010; 29(8): 914-56. PMID 20643330
174. Velleca A, Shullo MA, Dhital K, et al. The International Society for Heart and Lung Transplantation (ISHLT) guidelines for the care of heart transplant recipients. *J Heart Lung Transplant*. May 2023; 42(5): e1-e141. PMID 37080658
175. Kobashigawa J, Colvin M, Potena L, et al. The management of antibodies in heart transplantation: An ISHLT consensus document. *J Heart Lung Transplant*. May 2018; 37(5): 537-547. PMID 29452978
176. Zheng XL, Vesely SK, Cataland SR, et al. ISTH guidelines for treatment of thrombotic thrombocytopenic purpura. *J Thromb Haemost*. Oct 2020; 18(10): 2496-2502. PMID 32914526
177. Rovin BH, Adler SG, Barratt J, et al. KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases. *Kidney Int*. Oct 2021; 100(4S): S1-S276. PMID 34556256



178. Rovin BH, Ayoub IM, Chan TM, et al. KDIGO 2024 Clinical Practice Guideline for the management of LUPUS NEPHRITIS. *Kidney Int.* Jan 2024; 105(1S): S1-S69. PMID 38182286
179. Floege J, Jayne DRW, Sanders JF, et al. KDIGO 2024 Clinical Practice Guideline for the Management of Antineutrophil Cytoplasmic Antibody (ANCA)-Associated Vasculitis. *Kidney Int.* Mar 2024; 105(3S): S71-S116. PMID 38388102
180. Narayanaswami P, Sanders DB, Wolfe G, et al. International Consensus Guidance for Management of Myasthenia Gravis: 2020 Update. *Neurology.* Jan 19 2021; 96(3): 114-122. PMID 33144515
181. National Institute for Health and Care Excellence (NICE). Multiple sclerosis in adults: management [NG220]. 2022; <https://www.nice.org.uk/guidance/ng220>. Accessed January 6, 2025.
182. Tjnnfjord E, Holme PA, Darne B, et al. Long-term outcomes of patients treated with rituximab as second-line treatment for adult immune thrombocytopenia - Follow-up of the RITP study. *Br J Haematol.* 2020;191(3):460-465. doi:10.1111/bjh.16672
183. Sanchez-Alamo B, Schirmer JH, Hellmich B, et al. Systematic literature review informing the 2022 update of the EULAR recommendations for the management of ANCA-associated vasculitis (AAV): Part 2 - Treatment of eosinophilic granulomatosis with polyangiitis and diagnosis and general management of AAV. *RMD Open.* Jun 2023; 9(2). PMID 37349121
184. Canzian A, Venhoff N, Urban ML, et al. Use of Biologics to Treat Relapsing and/or Refractory Eosinophilic Granulomatosis With Polyangiitis: Data From a European Collaborative Study. *Arthritis Rheumatol.* Mar 2021; 73(3): 498-503. PMID 33001543
185. Covic A, Caruntu ID, Burlacu A, et al. Therapeutic Potential of Rituximab in Managing Hepatitis C-Associated Cryoglobulinemic Vasculitis: A Systematic Review. *J Clin Med.* Oct 27 2023; 12(21). PMID 37959271
186. Maher TM, Tudor VA, Saunders P, et al. Rituximab compared to intravenous cyclophosphamide in adults with connective tissue disease-associated interstitial lung disease: the RECITAL RCT. Southampton (UK): National Institute for Health and Care Research; February 2024.
187. Rasmussen C, Gérard L, Fadlallah J, et al. Higher rate of progression in HIV- than in HIV+ patients after rituximab for HHV8+ multicentric Castleman disease. *Blood Adv.* Sep 26 2023; 7(18): 5663-5669. PMID 37288720
188. Gliga S, Orth HM, Lübke N, et al. Multicentric Castleman's disease in HIV patients: a single-center cohort diagnosed from 2008 to 2018. *Infection.* Oct 2021; 49(5): 945-951. PMID 33945103
189. Doolan G, Faizal NM, Foley C, et al. Treatment strategies for Sjögren's syndrome with childhood onset: a systematic review of the literature. *Rheumatology (Oxford).* Mar 02 2022; 61(3): 892-912. PMID 34289032
190. Roccatello D, Sciascia S, Naretto C, et al. A Prospective Study on Long-Term Clinical Outcomes of Patients With Lupus Nephritis Treated With an Intensified B-Cell Depletion Protocol Without Maintenance Therapy. *Kidney Int Rep.* Apr 2021; 6(4): 1081-1087. PMID 33912758
191. Macrea M, Ghazipura M, Herman D, et al. Rituximab in Patients with Systemic Sclerosis-associated Interstitial Lung Disease: A Systematic Review and Meta-Analysis. *Ann Am Thorac Soc.* Feb 2024; 21(2): 317-327. PMID 37772987
192. Yilmaz DD, Borekci S, Musellim B. Comparison of the effectiveness of cyclophosphamide and rituximab treatment in patients with systemic sclerosis-related interstitial lung diseases: a retrospective, observational cohort study. *Clin Rheumatol.* Oct 2021; 40(10): 4071-4079. PMID 34056665
193. Filippini G, Kruja J, Del Giovane C. Rituximab for people with multiple sclerosis. *Cochrane Database Syst Rev.* Nov 08 2021; 11(11): CD013874. PMID 34748215
194. Cheshmavar M, Mirmosayyeb O, Badihian N, et al. Rituximab and glatiramer acetate in secondary progressive multiple sclerosis: A randomized clinical trial. *Acta Neurol Scand.* Feb 2021; 143(2): 178-187. PMID 32897569
195. Svenningsson A, Frisell T, Burman J, et al. Safety and efficacy of rituximab versus dimethyl fumarate in patients with relapsing-remitting multiple sclerosis or clinically isolated syndrome in Sweden: a rater-blinded, phase 3, randomised controlled trial. *Lancet Neurol.* Aug 2022; 21(8): 693-703. PMID 35841908



196. Magdalena C, Clarissa A, Sutandi N. Comparative Analysis of Treatment Outcomes in Patients with Neuromyelitis Optica Spectrum Disorder Treated with Rituximab, Azathioprine, and Mycophenolate Mofetil: A Systematic Review and Meta-analysis. *Innov Clin Neurosci*. 2022; 19(4-6): 51-64. PMID 35958974
197. Brauner S, Eriksson-Dufva A, Hietala MA, et al. Comparison Between Rituximab Treatment for New-Onset Generalized Myasthenia Gravis and Refractory Generalized Myasthenia Gravis. *JAMA Neurol*. Aug 01 2020; 77(8): 974-981. PMID 32364568
198. Nelke C, Schroeter CB, Stascheit F, et al. Eculizumab versus rituximab in generalised myasthenia gravis. *J Neurol Neurosurg Psychiatry*. May 2022; 93(5): 548-554. PMID 35246490
199. Xue C, Yang B, Xu J, et al. Efficacy and safety of rituximab in adult frequent-relapsing or steroid-dependent minimal change disease or focal segmental glomerulosclerosis: a systematic review and meta-analysis. *Clin Kidney J*. Apr 2021; 14(4): 1042-1054. PMID 34094516
200. Ma X, Fang L, Sheng L, et al. Rituximab treatment for refractory nephrotic syndrome in adults: a multicenter retrospective study. *Ren Fail*. Dec 2023; 45(1): 2237124. PMID 37482915
201. Heybeli C, Erickson SB, Fervenza FC, et al. Comparison of treatment options in adults with frequently relapsing or steroid-dependent minimal change disease. *Nephrol Dial Transplant*. Sep 27 2021; 36(10): 1821-1827. PMID 32918483
202. Lupus guideline. American College of Rheumatology. nd. <https://rheumatology.org/lupus-guideline>. Accessed January 6, 2025.

History

Date	Comments
01/13/15	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.
07/15/15	Minor edit. Removed link to policy 5.01.550.
07/01/16	Annual review, approved June 14, 2016. Medical necessity review criteria for site of service IV therapy added. Policy reformatted and reorganized.
08/01/16	Operational clarification. Clarified that medical necessity reviews for cancer diagnoses use policy 2.03.502.
11/01/16	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.
04/21/17	Minor edit. Introduction section revised for clarity.
07/01/17	Formatting edit; added hyperlink menu for Medical Necessity Criteria sections.
12/01/17	Annual Review, approved November 14, 2017. Policy updated with literature review through August 24, 2017; references 10, 26, 60, 75, 82, 98-102, 135-136, and 145 added. "Antineutrophil cytoplasmic antibody-associated vasculitides" added to second medically necessary statement for clarification. Indication for use in patients with pemphigus changed to coverage at initial diagnosis. Note added regarding subsequent doses using Rituxan Hycela. Divided sections by covered versus investigational. Removed codes J3490 and J3590.
02/14/18	Interim Review, approved February 13, 2018. Update hospital based outpatient coverage from 30 days to 90 days.



Date	Comments
11/01/18	Minor update, the Site of Service criteria was updated for clarity.
01/01/19	Annual Review, approved December 13, 2018. Policy updated with literature review through August 2018; references 23, 136-137, and 151-160 added; references 28 and 45 updated. Idiopathic membranous nephropathy was added to medical necessary statement. Added new HCPCS codes J9311 and J9312 (new codes effective 1/1/19).
04/01/19	Minor update, added Documentation Requirements section.
08/01/19	Interim Review, approved July 25, 2019. Added criteria for Truxima (rituximab-abbs) which is a biosimilar of Rituxan (rituximab). Added HCPCS code Q5115 to support Truxima. Title changed from "Rituxan (rituximab): Non-oncologic and Miscellaneous Uses" to "Rituximab: Non-oncologic and Miscellaneous Uses".
12/01/19	Annual Review, approved November 21, 2019. Policy updated with literature review through August 2019, references added. Policy statements unchanged
01/01/20	Interim Review, approved December 17, 2019, effective for dates of service on or after April 3, 2020, following provider notification. Rituxan (rituximab) and Ruxience (rixutimab-pvvr) noted as first-line products and Truxima (rituximab-abbs) as second line product. Added J3590 for Ruxience. Removed HCPCS code J9310 as it terminated 1/1/19.
07/01/20	Annual Review, approved June 18, 2020. Added Ruxience (rituximab-pvvr) to site-of-service review. Updated coverage criteria for the rituximab products for the treatment of rheumatoid arthritis by adding Rinvoq (upadacitinib) as a first-line treatment option. Changes to Ruxience for site of service review are effective for dates of service on or after October 2, 2020, following 90-day provider notification. Added code Q5119 for Ruxience, removed unlisted code J3590.
10/01/20	Interim Review, approved September 8, 2020. Updated coverage criteria for Rituxan (rituximab) and Ruxience (rituximab-pvvr) for the treatment of NMOSD requiring documentation of diagnosis of NMOSD and removing requirement to use an immunosuppressive drug prior to a rituximab product.
02/01/21	Annual Review, approved January 6, 2021. Added the biosimilar Riabni (rituximab-arrx) as a second line product. Added HCPCS code J3590.
07/01/21	Coding update, Added HCPCS code Q5123 and removed HCPCS code J3590.
07/01/22	Interim Review, approved June 14, 2022. Moved Truxima (rituximab-abbs) to being a preferred rituximab product. Updated coverage criteria for the non-preferred product Riabni (rituximab-arrx) to require the patient has had an adequate trial and failure with Rituxan, Ruxience, or Truxima. For the autoimmune hemolytic anemias updated coverage criteria from cold agglutination syndrome to cold agglutinin disease. Deleted effective date for HCPC code Q5123.
09/01/23	Annual Review, approved August 8, 2023. Changed the wording from "patient" to "individual" throughout the policy for standardization. Reviewed prescribing information of all drugs in the policy. Added preferred Humira biosimilars (Amjevita with NDC starting with 55513, Cyltezo LCF, Hyrimoz HCF and adamilumab- adaz HCF (Sandoz – unbranded) to the list of preferred products to be tried and failed prior to using preferred Rituxan products as second line therapy for the indication of Rheumatoid Arthritis. Effective January 1, 2024, following a 90 day provider



Date	Comments
	notification, following changes were made: Moved Ruxience to second line (non-preferred) agent, . Added HCPCS code J3590.
01/01/24	Interim Review, approved December 26, 2023. Updated preferred adalimumab products within the preferred rituximab product criteria to Humira (adalimumab), Cyltezo (adalimumab-adbm), Hyrimoz (adalimumab-adaz) (Sandoz) [NDCs starting with 61314], adalimumab-adaz (Hyrimoz unbranded) and adalimumab-adbm (Cyltezo unbranded).
05/01/24	Annual Review, approved April 9, 2024. Clarified that Humira (adalimumab) (AbbVie) [NDCs starting with 00074] is the preferred Humira product for rheumatoid arthritis.
07/01/24	Interim Review, approved June 11, 2024. Added Simlandi (adalimumab-ryvk) and adalimumab-ryvk (Simlandi unbranded) as preferred products. Added Simlandi to HCPCS code J3590.
10/01/24	Interim Review, approved September 10, 2024. The following policy changes are effective January 3, 2025, following a 90-day provider notification. Changed Ruxience (rituximab-pvvr) to a preferred product. Changed Rituxan (rituximab) and Rituxan Hycela (rituximab and hyaluronidase human) to non-preferred products. Updated coverage criteria for Riabni (rituximab-arrx), Rituxan, and Rituxan Hycela to require the individual has had an adequate trial and failure with Ruxience or Truxima. Updated Hyrimoz (Sandoz) (adalimumab-adaz) [NDCs starting with 61314] from a preferred product to a non-preferred product.
01/01/25	Interim Review, approved December 23, 2024. Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing information. Added the following note to the rheumatoid arthritis criteria regarding the preferred adalimumab product list: This list of preferred adalimumab products does not apply to one Open formulary (Formulary ID: 6062; Rx Plan F1) and one Incentive formulary (Formulary ID: 6064; Rx Plan G3). The preferred adalimumab products for members with these custom Open and Incentive formulary plans are the following: Adalimumab-adaz (Hyrimoz unbranded), adalimumab-adbm (Cyltezo unbranded), adalimumab-ryvk (Simlandi unbranded), Cyltezo (adalimumab-adbm), Humira (adalimumab) (AbbVie) [NDCs starting with 00074], and Simlandi (adalimumab-ryvk). More details can be found in policy 5.01.647 Medical Necessity Criteria for Custom Incentive and Open Formularies. Please check the member Plan booklet or member ID card to determine whether this list of preferred adalimumab products applies.
02/01/25	Annual Review, approved January 27, 2025. Policy updated to indicate that Site of Service Medical Necessity criteria does not apply to Alaska fully-insured members; only Medical Necessity criteria for the infusion drug applies pursuant to Alaska HB 226 (link added). Clarified that non-formulary exception review authorizations for all drugs listed in this policy may be approved up to 12 months. Added an exception to the site-



Date	Comments
	of-service requirements for certain individuals receiving treatment for cytokine release syndrome (CRS).
03/01/25	Interim Review, approved February 11, 2025. The following policy changes are effective July 1, 2025, following a 90-day provider notification. Removed Humira (adalimumab) (AbbVie) [NDCs starting with 00074] as a first-line step therapy option for the rheumatoid arthritis criteria.

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). ©2025 Premera All Rights Reserved.

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