| Reference number(s) |
| --- |
| 2501-A |

# Standard Medicare Part B Management Rituximab Products

## Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over the counter (OTC) products are not included unless otherwise stated.

| Brand Name | Generic Name |
| --- | --- |
| Rituxan | rituximab |
| Ruxience | rituximab-pvvr |
| Truxima | rituximab-abbs |
| Riabni | rituximab-arrx |

## Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

### FDA-Approved Indications[1,2,8,9]

Rituxan is indicated for the treatment of pediatric patients aged 6 months and older with previously untreated, advanced stage, CD20-positive diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma (BL), Burkitt-like lymphoma (BLL) or mature B-cell acute leukemia (B-AL) in combination with chemotherapy.

Rituxan is indicated for the treatment of granulomatosis with polyangiitis (GPA) (Wegener's Granulomatosis) and Microscopic Polyangiitis (MPA) in pediatric patients 2 years of age and older in combination with glucocorticoids.

Rituxan, Ruxience, Truxima, and Riabni are indicated for:

- Non-Hodgkin's Lymphoma (NHL) in adult patients with:

  - Relapsed or refractory, low-grade or follicular, CD20-positive, B-cell NHL as a single agent
  - Previously untreated follicular, CD20-positive, B-cell NHL in combination with first line chemotherapy and, in patients achieving a complete or partial response to a rituximab product in combination with chemotherapy, as single-agent maintenance therapy
  - Non-progressing (including stable disease), low-grade, CD20-positive, B-cell NHL, as a single agent after first-line CVP (cyclophosphamide, vincristine, and prednisone) chemotherapy
  - Previously untreated diffuse large B-cell, CD20-positive NHL in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or other anthracycline-based chemotherapy regimens
- Chronic lymphocytic leukemia (CLL), in combination with fludarabine and cyclophosphamide (FC), for the treatment of adult patients with previously untreated and previously treated CD20-positive CLL.
- Granulomatosis with Polyangiitis (Wegener's Granulomatosis) and Microscopic Polyangiitis, in combination with glucocorticoids in adult patients.
- Rheumatoid Arthritis (RA) in combination with methotrexate in adult patients with moderately-to severely-active RA who have inadequate response to one or more TNF antagonist therapies.
- Moderate to severe pemphigus vulgaris in adult patients.

Ruxience, Truxima, and Riabni are indicated for treatment of adult patients with moderate to severe pemphigus vulgaris in combination with glucocorticoids.

# Compendial Uses

- B-cell lymphoma[3-6]
  - Human Immunodeficiency Virus (HIV) related B-cell lymphoma[3]
  - Burkitt lymphoma[3-5]
  - Castleman's disease[3]
  - Diffuse large B-cell lymphoma[3]
  - High grade B-cell lymphoma (including high-grade B-cell lymphoma with translocations of MYC and BCL2 and/or BCL6 [double/triple hit lymphoma], high-grade B-cell lymphoma, not otherwise specified)[3]
  - Histological transformation of indolent lymphomas to diffuse large B-cell lymphoma[3]
  - Histological transformation of indolent lymphomas to high-grade B-cell lymphoma with MYC and BCL6 without BCL2 rearrangements[3]
  - Follicular lymphoma[3]
  - Mantle cell lymphoma[3,4]
  - Marginal zone lymphoma (nodal, extranodal [gastric and non-gastric mucosa associated lymphoid tissue (MALT) lymphoma], splenic )[3]
  - Post-transplant lymphoproliferative disorder (PTLD)[3,4]
  - Pediatric aggressive mature B-cell lymphomas[3]
  - B-cell lymphoblastic lymphoma[8]

  - Primary Mediastinal Large B-Cell Lymphoma[3]
- Malignant ascites, in advanced low-grade non-Hodgkin lymphoma[4]
- B-cell acute lymphoblastic leukemia (ALL)[3]
- CLL/small lymphocytic lymphoma (SLL)[3]
- Hairy cell leukemia[3,4,6]
- Rosai-Dorfman disease
- Hodgkin's lymphoma, nodular lymphocyte-predominant[3,4]
- Hodgkin's lymphoma, CD20-positive, relapsed or progressive[4]
- Primary cutaneous B-cell lymphoma[3,4]
- Central nervous system (CNS) cancers
  - Leptomeningeal metastases from lymphomas[3]
  - Primary CNS lymphoma[3]
- Waldenström's macroglobulinemia/lymphoplasmacytic lymphoma/Bing-Neel syndrome[31,4,6]
- Rheumatoid arthritis, moderate or high disease activity despite disease-modifying anti-rheumatic drug (DMARD) monotherapy[4,7]
- Autoimmune hemolytic anemia[4]
- Immune or idiopathic thrombocytopenic purpura (ITP), as initial therapy[4]
- Immune or idiopathic thrombocytopenic purpura (ITP), relapsed/refractory to standard therapy (e.g., corticosteroids, immune globulin)[4,6]
- Thrombotic thrombocytopenic purpura[4]
- Relapsing-remitting multiple sclerosis[4]
- Primary progressive multiple sclerosis[4]
- Myasthenia gravis, refractory to standard therapy (e.g., corticosteroids, immunosuppressants)[4]
- Systemic lupus erythematosus (SLE), refractory to standard therapy (e.g., corticosteroids, immunosuppressants)[4]
- Sjögren's syndrome[4]
- Chronic graft-versus-host disease (GVHD)[4]
- Prevention of Epstein-Barr virus (EBV)-related PTLD in hematopoietic stem cell transplant in (HSCT) recipients[4]
- Evans syndrome[4]
- Nephrotic syndrome, refractory to standard therapy (e.g., corticosteroids, immunosuppressants)[4]
- Acquired factor VIII deficiency (acquired hemophilia A)[4]
- Idiopathic inflammatory myopathy, refractory[4]
- Immune checkpoint inhibitor-related toxicities[4]
- Allogeneic transplant conditioning[3]
- Lung disease with systemic sclerosis[4]
- Thyroid eye disease (moderate to severe)[4]
- Neuromyelitis optica (i.e., neuromyelitis optica spectrum disorder, NMOSD, Devic disease)[4]
- Solid organ transplant[4]
- Severe, refractory polyarteritis nodosa[4]
- Membranous nephropathy[41]
- Susac syndrome[40.41]

- Non-infectious scleritis[42]

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

# Coverage Criteria

## Rheumatoid arthritis[1,2,4,7]

Authorization of 12 months may be granted for treatment of rheumatoid arthritis when either of the following criteria are met.

- The member has previously received treatment with a biologic or targeted synthetic DMARD (e.g., TNF inhibitor, JAK inhibitor) indicated for the treatment of rheumatoid arthritis.
- The member has had an inadequate response to methotrexate or leflunomide or there is a clinical reason to avoid treatment with methotrexate or leflunomide (e.g., renal or hepatic impairment).

## Oncologic indications[1-6,9]

Oncologic disorders must be CD20-positive as confirmed by testing or analysis to identify the CD20 protein on the surface of the B-cell.

### B-cell lymphoma[1-6,8,9]

Authorization of 12 months may be granted for treatment of any of the following indications:

- HIV-related B-cell lymphoma
- Burkitt lymphoma
- Castleman's disease
- Diffuse large B-cell lymphoma
- High grade B-cell lymphoma (including high-grade B-cell lymphoma with translocations of MYC and BCL2 and/or BCL6 [double/triple hit lymphoma], high-grade B-cell lymphoma, not otherwise specified)
- Histological transformation of indolent lymphomas to diffuse large B-cell lymphoma
- Histological transformation of indolent lymphomas to high-grade B-cell lymphoma with MYC and BCL6 without BCL2 rearrangements
- Follicular lymphoma
- Mantle cell lymphoma
- Marginal zone lymphoma (nodal, extranodal [gastric and non-gastric MALT], splenic )
- Post-transplant lymphoproliferative disorder
- Pediatric aggressive mature B-cell lymphomas
- B-cell lymphoblastic lymphoma
- Primary Mediastinal Large B-Cell Lymphoma

### Malignant ascites[5]

Authorization of 12 months may be granted for treatment of malignant ascites in patients with advanced low-grade non-Hodgkin lymphoma

### B-cell acute lymphoblastic leukemia (ALL)[3]

Authorization of 12 months may be granted for treatment of B-cell ALL.

### Chronic lymphocytic leukemia/Small lymphocytic lymphoma[1-3,8,9]

Authorization of 12 months may be granted for treatment of CLL/SLL.

### Hairy cell leukemia[3]

Authorization of 12 months may be granted for treatment of hairy cell leukemia.

### Hodgkin's lymphoma[3,4]

Authorization of 12 months may be granted for treatment of any of the following indications:

- Nodular lymphocyte-predominant Hodgkin's lymphoma
- CD20-positive relapsed or progressive Hodgkin's lymphoma

### Primary cutaneous B-cell lymphoma[3]

Authorization of 12 months may be granted for treatment of primary cutaneous B-cell lymphoma.

### Central nervous system (CNS) cancers[3]

Authorization of 12 months may be granted for treatment of any of the following indications:

- Leptomeningeal metastases from lymphomas
- Primary CNS lymphoma

### Waldenström's macroglobulinemia/lymphoplasmacytic lymphoma/Bing-Neel syndrome[3,4]

Authorization of 12 months may be granted for treatment of Waldenström's macroglobulinemia/lymphoplasmacytic lymphoma or Bing-Neel syndrome.

### Rosai-Dorfman disease[3]

Authorization of 12 months may be granted for the treatment of Rosai-Dorfman disease.

## Hematologic indications[4-6]

Authorization of 12 months may be granted for treatment of any of the following indications:

- Autoimmune hemolytic anemia
- Immune or idiopathic thrombocytopenic purpura
- Thrombotic thrombocytopenic purpura
- Evans syndrome
- Acquired factor VIII deficiency (acquired hemophilia A)

## Multiple sclerosis[4]

Authorization of 12 months may be granted for treatment of relapsing-remitting multiple sclerosis and primary progressive multiple sclerosis.

## Myasthenia gravis[4]

Authorization of 12 months may be granted for treatment of myasthenia gravis that is refractory to standard therapy (e.g., corticosteroids, immunosuppressants) or if there is a clinical reason to avoid standard therapy.

## Systemic lupus erythematosus[6]

Authorization of 12 months may be granted for treatment of systemic lupus erythematosus that is refractory to standard therapy (e.g., corticosteroids, immunosuppressants) or if there is a clinical reason to avoid standard therapy.

## Granulomatosis with polyangiitis (Wegener's granulomatosis) and microscopic polyangiitis[1,2,9]

Authorization of 12 months may be granted for treatment of granulomatosis with polyangiitis and microscopic polyangiitis.

## Sjögren's syndrome[4]

Authorization of 12 months may be granted for treatment of Sjögren's syndrome.

## Nephrotic syndrome[4]

Authorization of 12 months may be granted for treatment of nephrotic syndrome (e.g., minimal change disease) that is refractory to standard therapy (e.g., corticosteroids, immunosuppressants) or if there is a clinical reason to avoid standard therapy.

## Idiopathic inflammatory myopathy[4]

Authorization of 12 months may be granted for treatment of refractory idiopathic inflammatory myopathy.

## Immune checkpoint inhibitor-related toxicities[3]

Authorization of 3 months may be granted for treatment of immune checkpoint inhibitor-related toxicities.

## Lung disease with systemic sclerosis[4]

Authorization of 12 months may be granted for the treatment of lung disease with systemic sclerosis that is refractory to standard therapy (e.g., cyclophosphamide, mycophenolate) or if there is a clinical reason to avoid standard therapy.

## Thyroid eye disease (moderate to severe)[4]

Authorization of 12 months may be granted for the treatment of moderate to severe thyroid eye disease (excluding patients with risk for dysthyroid optic neuropathy) that is refractory to standard therapy (e.g., IV glucocorticoids) or if there is a clinical reason to avoid standard therapy.

## Solid organ transplant[4]

Authorization of 12 months may be granted for prevention and treatment of antibody mediated rejection in solid organ transplant.

## Membranous nephropathy[39]

Authorization of 12 months may be granted for treatment of membranous nephropathy when the member is at moderate to high risk for disease progression.

## Other indications[1,3,4,6,12,40-42]

Authorization of 12 months may be granted for treatment of any of the following indications:

- Chronic GVHD
- Prevention of EBV-related PTLD in HSCT recipients
- Pemphigus vulgaris
- As part of a non-myeloablative conditioning regimen for allogeneic transplant
- Neuromyelitis optica (i.e., neuromyelitis optica spectrum disorder [NMOSD], Devic disease)
- Severe, refractory polyarteritis nodosa
- Susac syndrome
- Non-infectious scleritis

# Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 3 months may be granted for the diagnosis of immune checkpoint inhibitor-related toxicities when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication.

- The member is receiving benefit from therapy.

Authorization for 12 months may be granted for all diagnoses (except immune checkpoint inhibitor-related toxicities) when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication.
- The requested medication is being used to treat an indication in the coverage criteria section.
- The member is receiving benefit from therapy.

# Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Rituxan, Ruxience, Truxima, and Riabni.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology
- NCCN Guideline: Histiocytic neoplasms
- NCCN Guideline: Hairy cell leukemia
- NCCN Guideline: Waldenstrom macroglobulinemia/lymphoplasmacytic lymphoma
- NCCN Guideline: Hodgkin lymphoma
- NCCN Guideline: Hematopoietic cell transplantation
- NCCN Guideline: B-cell lymphoma
- Diagnosis and management of acquired coagulation inhibitors: a guideline from UKHCDO
- Guidelines on the management of drug-induced immune and secondary autoimmune, haemolytic anemia
- Rituximab in the treatment of refractory adult and juvenile dermatomyositis and adult polymyositis: a randomized, placebo-phase trial
- American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia
- American Society of Hematology 2019 guidelines for immune thrombocytopenia
- French recommendations for the management of systemic sclerosis
- Is rituximab effective for systemic sclerosis? A systematic review and meta-analysis
- Kidney Disease Improving Global Outcomes (KDIGO) Glomerular Diseases Working Group: KDIGO clinical practice guideline for the management of glomerular diseases
- Myasthenia gravis: Association of British Neurologists' management guidelines
- Canadian Cardiovascular Society/Canadian Cardiac Transplant Network position statement on heart transplantation: patient eligibility, selection, and post-transplantation care
- Rituximab effectiveness and safety for treating primary Sjogren's syndrome (pSS): systematic review and meta-analysis

- Efficacy and safety of rituximab in relapsing-remitting multiple sclerosis: a systematic review and metanalysis
- Efficacy and safety of different doses and retreatment of rituximab: a randomized, placebo-controlled trial in patients who are biological naïve with active rheumatoid arthritis in an inadequate response to methotrexate (SERENE)
- Efficacy and safety of various repeat treatment dosing regimens of rituximab in patients with active rheumatoid arthritis: results of a phase III randomized study (MIRROR)
- Efficacy and safety of rituximab in the treatment of non-renal systemic lupus erythematosus
- 2019 update of EULAR recommendations for the management of systemic lupus erythematosus
- A phase 2 study of the safety and efficacy of rituximab with plasma exchange in acute acquired thrombotic thrombocytopenic purpura
- Efficacy and safety of first-line rituximab in severe, acquired thrombotic thrombocytopenic purpura with suboptimal response to plasma exchange: experience of the French Thrombotic Microangiopathic Reference Center
- 2021 European Group on Grave's orbitopathy (EUGOGO) clinical practice guidelines for the medical management of Grave's orbitopathy
- Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases
- Diagnostic Criteria and Treatment Algorithm for Susac Syndrome
- Rituximab for non-infectious uveitis and scleritis

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Rituxan, Ruxience, Truxima and Riabni are covered in addition to the following:

- B-cell lymphoma
    - Human Immunodeficiency Virus (HIV) related B-cell lymphoma
    - Burkitt lymphoma
    - Castleman's disease
    - Diffuse large B-cell lymphoma
    - High grade B-cell lymphoma (including high-grade B-cell lymphoma with translocations of MYC and BCL2 and/or BCL6 [double/triple hit lymphoma], high-grade B-cell lymphoma, not otherwise specified)
    - Histological transformation of indolent lymphomas to diffuse large B-cell lymphoma
    - Histological transformation of indolent lymphomas to high-grade B-cell lymphoma with MYC and BCL6 without BCL2 rearrangements
    - Follicular lymphoma
    - Mantle cell lymphoma
    - Marginal zone lymphoma (nodal, extranodal {gastric and non-gastric mucosa associated lymphoid tissue (MALT) lymphoma}, splenic )
    - Post-transplant lymphoproliferative disorder (PTLD)
    - Pediatric aggressive mature B-cell lymphomas
    - B-cell lymphoblastic lymphoma
    - Primary Mediastinal Large B-Cell Lymphoma

- Malignant ascites in advanced low-grade non-Hodgkin lymphoma
- B-cell acute lymphoblastic leukemia (ALL)
- CLL/small lymphocytic lymphoma (SLL)
- Hairy cell leukemia
- Rosai-Dorfman disease
- Hodgkin's lymphoma, lymphocyte-predominant
- Hodgkin's lymphoma, CD20-positive, relapsed or progressive
- Primary cutaneous B-cell lymphoma
- Central nervous system (CNS) cancers
    - Leptomeningeal metastases from lymphomas
    - Primary CNS lymphoma
- Waldenström's macroglobulinemia/lymphoplasmacytic lymphoma/Bing-Neel syndrome
- Rheumatoid arthritis, moderate or high disease activity despite disease-modifying anti-rheumatic drug (DMARD) monotherapy
- Autoimmune hemolytic anemia
- Immune or idiopathic thrombocytopenic purpura (ITP), as initial therapy
- Immune or idiopathic thrombocytopenic purpura (ITP), relapsed/refractory to standard therapy (e.g., corticosteroids, immune globulin)
- Thrombotic thrombocytopenic purpura
- Relapsing-remitting multiple sclerosis
- Primary progressive multiple sclerosis
- Myasthenia gravis, refractory to standard therapy (e.g., corticosteroids, immunosuppressants)
- Systemic lupus erythematosus, refractory to standard therapy (e.g., corticosteroids, immunosuppressants)
- Sjögren's syndrome
- Chronic graft-versus-host disease (GVHD)
- Prevention of Epstein-Barr virus (EBV)-related PTLD in hematopoietic stem cell transplant in (HSCT) recipients
- Evans syndrome
- Nephrotic syndrome, refractory to standard therapy (e.g., corticosteroids, immunosuppressants)
- Acquired factor VIII deficiency (acquired hemophilia A)
- Idiopathic inflammatory myopathy, refractory
- Immune checkpoint inhibitor-related toxicities
- Allogeneic transplant conditioning
- Lung disease with systemic sclerosis
- Thyroid eye disease (moderate to severe)
- Neuromyelitis optica (i.e., neuromyelitis optica spectrum disorder, NMOSD, Devic disease)
- Solid organ transplant
- Severe, refractory polyarteritis nodosa
- Membranous nephropathy
- Susac Syndrome
- Non-infectious scleritis

# Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for the below indications can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

- B-cell lymphomas (human immunodeficiency virus (HIV)-related B-cell lymphoma, Burkitt lymphoma, Castleman's disease, diffuse large B-cell lymphoma, high grade B-cell lymphoma, histological transformation of indolent lymphomas to diffuse large B-cell lymphoma, histological transformation of indolent lymphomas to high-grade B-cell lymphoma with MYC and BCL6 without BCL2 rearrangements, follicular lymphoma, mantle cell lymphoma, marginal zone lymphoma, post-transplant lymphoproliferative disorder, pediatric aggressive mature B-cell lymphomas, B-cell lymphoblastic lymphoma, primary mediastinal large B-cell lymphoma)
- B-cell acute lymphoblastic leukemia
- CLL/SLL
- Hairy cell leukemia
- Rosai-Dorfman disease
- Hodgkin's lymphoma, lymphocyte-predominant
- Hodgkin's lymphoma, CD20-positive, relapsed or progressive
- Primary cutaneous B-cell lymphoma
- Leptomeningeal metastases from lymphomas
- CNS lymphomas
- Waldenstrom's macroglobulinemia/lymphoplasmacytic lymphoma/Bing-Neel syndrome

Support for using rituximab to treat malignant ascites in patients with advanced low-grade non-Hodgkin lymphoma can be found in a case report by Ng, Pagliuca and Mufti (2002). The 59-year-old man had achieved partial remission with modified CHOP (cyclophosphamide, doxorubicin, vinblastine, and prednisolone) chemotherapy every 3 weeks for 6 cycles followed by weekly IV rituximab for 4 weeks. Regular drainage of abdominal ascites was still required 8 weeks after IV rituximab. Intraperitoneal rituximab (375 mg/m2 in 250 mL of 5% dextrose over 4 hours) was administered every 3 days for 4 doses. The treatment was well tolerated, with no reported adverse events or significant changes in blood parameters. An abdominal computed tomography scan 3 weeks after intraperitoneal rituximab showed a marked regression of ascites. No ascites was detected with clinical examination and no additional drainage of ascites was required during the 8-month follow-up period.

Support for using rituximab to treat rheumatoid arthritis that continues to be of moderate or high disease activity despite DMARD monotherapy can be found in two studies. The addition of rituximab to methotrexate in patients with active rheumatoid arthritis (RA) despite methotrexate treatment significantly improved American College of Rheumatology (ACR)20 and ACR50 response rates at week 24 in the Study Evaluating Rituximab's Efficacy in MTX Inadequate Responders (SERENE), a multicenter, randomized, double-blind, placebo-controlled, phase 3 study (n=509). Eligible patients were 18 to 80 years old, had active RA for at least 6 months despite methotrexate treatment (10 to 25 mg/week) for at least 12 weeks,

and had not previously received biological treatment for RA. After a 2-week or longer washout of disease modifying antirheumatic drugs, during which patients continued stable dose methotrexate (10 to 25 mg/week) and folic acid (5 mg/week or greater), patients were randomized to IV therapy on days 1 and 15 with rituximab 500 mg (2 x500 group; n=167), rituximab 1000 mg (2 x 1000 group; n=170), or placebo (n=172); premedication for all 3 groups was methylprednisolone 100 mg IV. NSAIDs and stable dose corticosteroids (prednisolone less than or equal to 10 mg/day orally [or equivalent]) were allowed. Patients who were not in remission at week 24 (Disease Activity Score [28 joints]-erythrocyte sedimentation rate [DAS28-ESR] less than 2.6) and met safety criteria were eligible for open-label rituximab treatment with the randomized dose (or 2 doses of 500 mg for initial placebo assignment). Initiation of 1 non-biologic DMARD was allowed if a less than 20% improvement in tender joint count (JC) and swollen JC versus baseline was noted between weeks 16 and 23. At week 24, significantly more patients in the rituximab 2 x500 mg and rituximab 2 x 1000 mg groups than in the placebo group, respectively, achieved an ACR20 response (primary outcome; 54.5% and 50.6% vs 23.3%) and an ACR 50 response (26.3% and 25.9% vs 9.3%). In the rituximab 2 x 500 mg and rituximab 2 x 1000 mg groups compared with the placebo group, respectively, there were also significant improvements in clinical remission (9.6% and 9.4% vs 2.3%), European League Against Rheumatism (EULAR) good response (17.4% and 11.8% vs 4.7%), and EULAR moderate response (49.1% and 51.2% vs 29.1%). By week 48, 93.5% of the rituximab 2 x 500 mg group, 91.3% of the rituximab 2 x 1000 mg group, and 89.5% of the placebo group had received a second course of treatment. At week 48, levels of disease activity were maintained or improved, with ACR20 response rates at 55.7% for rituximab 2 x 500 mg and 57.6% for rituximab 2 x 1000 mg and ACR50 response rates at 32.9% and 34.1%, respectively. Adverse effects to week 24 were reported in 77% of the rituximab 2 x 500 mg group, 76% of the rituximab 2 x 1000 mg group, and 74% of the placebo group, and included infusion-related reactions with the day 1 infusion (19%, 25%, and 14%) and with the day 15 infusion (7%, 6%, and 8%). The overall infection rate per 100 patient-years was 138.13 in the rituximab 500 mg group, 120.45 in the rituximab 1000 mg group, and 159 in the placebo group with a serious infection rate of 1.26, 2.46, and 8.83, respectively. Adverse effects to 48 weeks with rituximab 2 x 500 mg and rituximab 2 x 1000 mg were similar to the rates at 24 weeks.

An American College of Rheumatology (ACR)20 response was achieved in 64% to 72% of patients with rheumatoid arthritis (RA) at 48 weeks after treatment with 1 of 3 rituximab regimens administered initially and at 24 weeks plus methotrexate, in the multicenter, randomized, double-blind, phase 3 MIRROR trial (n=346). Eligible patients had a diagnosis of RA for at least 6 months, had active disease despite methotrexate therapy (10 to 25 mg/week) for at least 12 weeks (stable dose for at least 4 weeks), and had previously received no more than 1 biological agent for RA. Patients continued stable methotrexate doses of 10 to 25 mg/week during the study and were randomized to 1 of 3 rituximab regimens: 2 x 500 mg group, who received two 500 mg doses initially and at week 24 (n=134; mean age, 53.6 years); dose escalation group, who received two 500 mg doses initially and two 1000 mg doses at week 24 (n=119; mean age, 52.3 years); and 2 x 1000 mg group, who received two 1000 mg doses initially and at week 24 (n=93; mean age 51.3 years). Methylprednisolone 100 mg IV was administered before all rituximab infusions. Folic acid (5 mg/week), NSAIDs, oral glucocorticoids (10 mg/day or less), and intra-articular glucocorticoid injections of no more than 1 joint per 24 weeks were allowed; additional nonbiological and biological disease modifying antirheumatic drugs were not allowed. ACR20 response rates at 48 weeks were not significantly different between the rituximab 2 x 500 mg group and the dose escalation group (primary outcome; 64% for both groups) or between the rituximab 2 x 500 mg group and the rituximab 2 x

1000 mg group (64% vs 72%). ACR20 response rates at 48 weeks were similar in patients who had received a previous biological agent and patients who had not (65% and 67%, respectively). There were no significant differences among the 2 x 500 mg group, the dose escalation group, and the 2 x 1000 mg group, respectively, at 48 weeks in ACR50 response rates (39%, 39%, and 48%) or ACR70 response rates (20%, 19%, 23%). A moderate or good European League Against Rheumatism (EULAR) response was achieved by significantly more patients in the rituximab 2 x 1000 mg group than in the rituximab 2 x 500 mg group (89% vs 73%) or the dose escalation group (89% vs 72%). Disease Activity Score (28 joints)-erythrocyte sedimentation rate (DAS28-ESR) remission (DAS28-ESR less than 2.6) was achieved by 9% in the rituximab 2 x 500 mg group, by 13% in the dose escalation group, and by 19% in the rituximab 2 x 1000 mg group. Adverse effects were similar in all 3 treatment groups, occurred in 89% to 91% of patients, and included infusion-related reactions (30% to 39%) and infections (56% to 65%).

Jager et al supports using rituximab in the treatment of autoimmune hemolytic anemia. In patients with symptomatic, primary cold agglutinin disease, first-line treatment consists of rituximab alone, or rituximab plus bendamustine in fit patients. Rituximab plus bendamustine should be given if not previously used, or in patients who responded to it as first-line therapy and at least 2 years have passed since treatment. Rituximab monotherapy may be repeated in patients who previously responded for at least 1 year. Rituximab plus fludarabine is an option for fit, elderly patients. Corticosteroids remain first-line therapy for warm-AIHA, while the addition of rituximab should be considered early in severe cases and if no prompt response to steroids is achieved.

A systematic review by Liu et al identified 2 randomized studies of rituximab in patients with newly-diagnosed warm autoimmune hemolytic anemia. The addition of rituximab to a glucocorticoid significantly increased the likelihood of a complete hematological response at 12 months compared with glucocorticoid alone, but there were no significant improvements on the likelihood of a complete response at 6 months, partial responses at 6 or 12 months, or red blood cell requirement at 2, 6, or 12 months.

Support for using rituximab to treat immune thrombocytopenia is supported in treatment guidelines. The American Society of Hematology has published guidelines on the treatment of immune thrombocytopenia (Neunert et al). Rituximab may be considered in patients who have failed first-line therapy with conventional doses of corticosteroids, IV immune globulin, or splenectomy and who are at risk of bleeding. In 19 reports, the pooled estimate of overall platelet count response in 313 patients was 62.5%; however, durability of response varied. In 1 study of 306 patients, severe or life-threatening complications associated with rituximab occurred in 3.3%. Rituximab may be considered in patients with ITP who continue to have significant bleeding despite first-line therapy with corticosteroids or IV immune globulin.

As initial treatment of newly diagnosed ITP, corticosteroids alone rather than corticosteroids with rituximab is suggested (evidence with very low certainty). An initial course of corticosteroids with rituximab may be preferred if the potential for remission is valued higher than the potential for adverse events with rituximab.

Rituximab may also be considered as an alternative to splenectomy in patients with chronic ITP and in those who respond poorly to splenectomy. In 1 study, only 8 of 36 patients maintained platelet counts greater than 50 x 109/L at the 1-year follow-up after weekly doses of rituximab; however, other studies have demonstrated higher response rates, particularly when the rituximab dose was doubled after lack of response. Serum sickness was reported in some patients.

Froissart et al for the French Thrombotic Microangiopathies Reference Center, supports using rituximab for thrombotic thrombocytopenic purpura. The time to a durable remission was significantly shorter in patients with thrombotic thrombocytopenic purpura (TTP) who had a suboptimal response to therapeutic plasma exchange (TPE) and received rituximab compared with historical controls who did not receive rituximab; however, the mean plasma volume required to achieve durable remission did not differ significantly between the 2 groups in a prospective cohort study (n=74). Patients with thrombotic microangiopathy (Coombs-negative microangiopathic hemolytic anemia, acute peripheral thrombocytopenia [platelet count less than 150 x 109/L], and absence of identifiable cause for thrombocytopenia and microangiopathic hemolytic anemia) and mild renal involvement (less than 2.26 mg/dL) were diagnosed with TTP, with a definitive diagnosis confirmed by ADAMTS13 activity of less than 10%. Patients with hemolytic uremic syndrome, rituximab therapy for a previous TTP episode, or detectable ADAMTS13 activity after rituximab therapy were excluded. Patients with a suboptimal response to daily TPE (plasma volume, 1.5 predicted plasma volume for first procedure, 1 times predicted plasma volume thereafter until remission, followed by maintenance TPE tapered over 3 weeks) received rituximab 375 mg/m2 on the day of diagnosis of suboptimal response (day 0), day 3, day 7, and day 14 with premedication of dexchlorpheniramine 10 mg IV and acetaminophen 1 g IV. Patients without active infection received glucocorticoid therapy (1 mg/kg/day) for 3 weeks; patients not receiving glucocorticoids received methylprednisolone 30 mg IV. Suboptimal response was defined as an exacerbation (worsening neurologic manifestations, platelet count of less than 100 x 109/L for at least 2 days, or platelet count decrease of more than one-third the highest count for at least 2 days) or TTP refractory to TPE (platelet count after 4 days of TPE less than 2 times baseline with LDH persistently greater than ULN). Durable remission was defined as complete response (resolution of neurologic manifestations and platelet count greater than 150 x 109/L for at least 2 days) with no thrombocytopenia or clinical worsening during at least 30 days after first day of platelet recovery (including time on maintenance TPE). In the rituximab group (n=21; mean age, 36.8 +/- 11 years; glucocorticoid therapy, 71%; cytotoxic therapy, 0%; mean follow-up, 33 +/- 17.4 months) compared with historical controls (n=53; mean age, 41.7 +/- 16 years; glucocorticoid therapy, 79%; vincristine, n=17; vincristine and cyclophosphamide, n=3; mean follow-up, 35.3 +/- 28.5 months), platelet count recovery time (coprimary outcome) was significantly shorter (p=0.03). At day 35, significantly more patients (100% vs 78%; p less than 0.02) had achieved a durable remission; durable remission was achieved at a mean of 12 +/- 6.7 days after rituximab initiation. There were no significant differences between the rituximab group and the historical controls in mean plasma volume required to achieve a durable remission (coprimary outcome; 891 +/- 402 vs 999 +/- 583 mL/kg; p=0.67), exacerbation rate (2 of 21 vs 16 of 53; p less than 0.08), or relapse rate (within first year, 0% vs 9.4% [p=0.34]; after first year, 15.8% vs not reported [p=0.68]). In the rituximab group, mean peripheral B-cell counts were decreased by 80% compared with baseline on day 4; decreased to 1% of baseline by day 8; undetectable at month 3; less than 5% of baseline after 3 and 6 months; and greater than 10% of baseline after 12 months. In an analysis of the rituximab group (n=21) compared with historical controls with available data (n=19), ADAMTS13 activity was significantly higher after 1, 3, 6, and 9 months, but was similar at 12 months, and ADAMTS13 antibody titers were significantly lower at 3, 6, and 9 months and similar at 12 months. No severe adverse effects, hypogammaglobulinemia, or clinically relevant infections were reported with rituximab.

Support for using rituximab to treat multiple sclerosis can be found in two randomized trials.

A randomized, controlled trial and systematic review support using rituximab to treat relapsing-remitting multiple sclerosis. Svenningsson et al found rituximab therapy significantly reduced risk of relapse at 24 months compared with dimethyl fumarate in adults with treatment-naive relapsing remitting multiple sclerosis in the randomized, phase 3 RIFUND-MS trial. Toxicity was consistent with known safety profiles of each agent.

In a systematic review and meta-analysis by Tian et al in patients with relapsing-remitting multiple sclerosis, rituximab significantly reduced both the annualized relapse rate and the functional burden of disease, as measured by the mean Expanded Disability Status Scale score. Relapse rates declined over duration of rituximab use but remained at less than 15% through 96 weeks. This compilation of studies is inclusive, down to reports of 10 or more patients, but methodological quality and overall heterogeneity of the studies may limit these findings.

Support for using rituximab for primary progressive multiple sclerosis can be found in a randomized trial of patients with a disease duration of at least one year (N=439) by Hawker et al. There was no significant difference in rate of confirmed disease progression (CDP) between rituximab (30.2%) and placebo (38.5%) at 96 weeks. However, patients receiving rituximab did experience significantly smaller increases in median T2 lesion volume compared with those receiving placebo (301.95 mm3 vs 809.5 mm3). Subgroup analyses demonstrated that time to CDP was significantly delayed with the administration of rituximab in patients younger than 51 years of age (HR, 0.52) and in those with gadolinium brain lesions at baseline (HR, 0.41). Additionally, patients less than 51 years of age with baseline gadolinium lesions experienced a 61.6% relative reduction in total T2 lesion volume accumulation with rituximab compared with 50.7% for patients 51 years or older with baseline gadolinium lesions. In an exploratory analysis the median increase from baseline to week 96 in the Multiple Sclerosis Functional Composite (MSFC) timed 25-foot walk was 0.9 seconds with rituximab versus 1.48 seconds with placebo. Safety follow-up through 122 weeks demonstrated that the incidence of adverse events was similar between treatment groups; mild to moderate infusion-related reactions were more common with rituximab but the incidence decreased with successive infusions.

Support for using rituximab to treat myasthenia gravis (MG) can be found in one published guideline and a large meta-analysis. According to the Association of British Neurologists, rituximab has a role in managing poorly responsive myasthenia gravis when treatment with azathioprine has failed or the patient cannot tolerate it.

Zhao and colleagues (2021) noted that MG is an autoimmune neuromuscular disease. Nearly 10 to 30% of patients with MG are refractory to conventional therapy; rituximab is increasingly used in autoimmune disorders. In a systematic review and meta-analysis, these researchers examined the safety and effectiveness of rituximab for the treatment of refractory MG. Studies published between January 1, 2000 and January 17, 2021 were searched in PubMed, Embase, Cochrane Library, and ClincalTrails.gov. Primary outcomes included proportion of patients achieving minimal manifestation status (MMS) or better and quantitative MG (QMG) score change from baseline. Secondary outcomes were glucocorticoids (GC) doses change from baseline and proportion of patients discontinuing oral immunosuppressants. A total of 24 studies involving 417 patients were included in the meta-analysis. An overall 64 % (95 % CI: 49 % to 77 %) of patients achieved MMS or better. The estimated reduction of QMG score was 1.55 (95 % CI: 0.88 to 2.22). The mean reduction of GC doses was 1.46 (95 % CI: 1.10 to 1.82). The proportion of patients

discontinuing oral immunosuppressants was 81 % (95 % CI: 66 % to 93 %). Subgroup analyses showed that the proportion of patients achieving MMS or better and discontinuing oral immunosuppressants was higher in MuSK-MG group than those in AChR-MG group. Improvement was more pronounced in patients with mild-to-moderate MG compared to those with severe MG. Moreover, the effectiveness appeared to be independent of the dose of rituximab. A total of 19.6% of patients experienced AEs, most of which were mild-to-moderate. Only 1 patient developed PML. The authors concluded that this systemic review and meta-analysis suggested that rituximab therapy could improve the PIS of a considerable number of patients with refractory MG to reach MMS or better with a good safety profile. It also exhibited a steroid-sparing effect. Furthermore, rituximab reduced QMG scores and the use of conventional oral immunosuppressants. The effectiveness was related to the patient's serotype and disease severity, but not to the doses of rituximab. These researchers stated that randomized controlled trials are needed to examine the effectiveness of rituximab in the treatment of refractory MG and to identify the characteristics of patients who might respond well to rituximab.

The authors stated that this study had several drawbacks. First, most of the studies included in the meta-analysis were observational studies, which might over-estimate the effectiveness of treatments compared with controlled trials. Second, these researchers could not compare the effectiveness of rituximab with other drugs since most of the included studies were single-arm. Third, the number of patients in each study was relatively small. In subgroup analysis, the number of cases in some studies was no more than 5, which resulted in great randomness of research results. Finally, the heterogeneity between studies was remarkable. There were many reasons for the high heterogeneity. Myasthenia gravis is a rare disease with high heterogeneity. Moreover, the rituximab regimen, follow-up duration and baseline characteristics of patients differed among studies. These investigators could not carry out meta-regression because some information was inaccessible in studies.

Support for using rituximab for systemic lupus erythematosus can be found in treatment guidelines. The European League Against Rheumatism (EULAR) recommendations for the management of systemic lupus erythematosus recommend rituximab as a treatment option for patients with organ-threatening SLE that is refractory to, or in patients with intolerance or contraindications to immunosuppressive agents. Additionally, a systematic review by Cobo-Ibanez et al found rituximab was safe and effective in patients with non-renal systemic lupus erythematosus, specifically disease activity, arthritis, thrombocytopenia, anti-dsDNA, and steroids-paring effect; long-term studies are needed.

Support for using rituximab for primary Sjogren's syndrome can be found in a published systematic review. Souza et al completed a systematic review and meta-analysis to review the literature available addressing using rituximab for primary Sjogren's syndrome. Four 24-week randomized trials in 276 adults with primary Sjogren's syndrome, a single course of rituximab 1 g IV on days 1 and 15 compared with placebo significantly improved lacrimal gland function using the lissamine green test (1 study), but no significant between-group difference using the Schirmer test (2 studies). Rituximab was associated with significant improvement in the salivary flow rate (low-quality evidence, 3 studies), but no significant difference in a 30% improvement in fatigue (3 studies), quality of life improvement (3 studies), or disease activity (2 studies). There was no significant between-group difference in serious adverse events.

Support for using rituximab for prophylaxis against Epstein-Barr virus (EBV) disease in patients who have received a hematopoietic stem cell transplant can be found in a guideline published by Tomblyn et al. To

prevent EBV-associated PTLD, high-risk patients (e.g., after T cell depletion, use of anti-T cell antibodies, umbilical cord blood transplants, and haplo identical transplants) should be assessed for EBV DNA load using a EBV PCR assay. Monitoring allows for preemptive immunosuppression reduction if feasible. If no response occurs with immunosuppression reduction, preemptive therapy with rituximab is recommended to prevent PTLD. Infusion of donor-derived, EBV-specific cytotoxic T-lymphocytes has shown some efficacy in the prophylaxis of EBV-lymphoma among recipients of T cell-depleted unrelated or mismatched allogeneic recipients. Other treatments that have been used include expanded donor-derived EBV-specific T cells to control blood EBV DNA levels and use of B cell depletion to decrease the risk of EBV PTLD. Due to lack of efficacy, prophylaxis or preemptive treatment with currently available antiviral agents is not recommended.

Support for using rituximab for Evans syndrome can be found in a guideline, small trials and a case report. The British Society for Haematology supports using rituximab as second-line therapy for primary Evans syndrome. Other second-line therapies include immunosuppressive drugs, danazol, splenectomy or vincristine.

Rituximab appears to effectively treat pediatric patients with refractory Evans syndrome based upon small, prospective, single-arm trials and case reports; however, long-term, randomized, controlled, clinical trials are not available to confirm safety in this population. Two prospective studies, one of severe immune thrombocytopenic purpura and one of autoimmune hemolytic anemia, contained subgroups of Evans patients who responded to treatment with rituximab based upon hematologic results from the entire cohort. Three Evans patients relapsed and were successfully retreated with rituximab. Safety data are inconclusive since adverse events (i.e., infusion reactions, bleeding, and serum sickness) were reported for the entire cohort, and it is unclear which of these occurred in the Evans subpopulation. Varicella infection requiring hospitalization was reported in one Evans syndrome patient after rituximab treatment. During post marketing surveillance, it has been reported that two adult patients died from progressive multifocal leukoencephalopathy (PML) while receiving rituximab for another autoimmune disease, systemic lupus erythematosus. PML was caused by reactivation of JC virus, and risk in the pediatric population is unknown.

Support for using rituximab for the treatment of nephrotic syndrome can be found in the KDIGO glomerular disease working group. In patients with frequently relapsing steroid-dependent minimal change disease, treatment with cyclophosphamide, rituximab, calcineurin inhibitors (cyclosporine, tacrolimus), or mycophenolic acid analogues (mycophenolate mofetil, sodium mycophenolate) is recommended rather than prednisone alone or no treatment. Rituximab has been associated with inducing remission in 65% to 100% of patients and has reduced the number of relapses, and the number of immunosuppressive drugs. However, the long-term efficacy and risks are unknown.

Support for using rituximab for acquired factor VIII deficiency (acquired hemophilia A) can be found in guidelines from UKHCDO. Rituximab can be considered as first-line therapy if standard immunosuppression is contraindicated but may have limited efficacy if used as a single agent. If there is no response within 3–5 weeks, second-line therapies should be considered. The most common second-line treatment is with rituximab combined with other agents. Alternative options are calcineurin inhibitors, multiple immunosuppressive agents and immune tolerance protocols.

Support for using rituximab for idiopathic inflammatory myopathy can be found in a randomized trial. Treatment with rituximab resulted in an 83% total rate of improvement and provided steroid-sparing effects after 44 weeks, despite not showing a difference between the randomized groups of "early" versus "late" rituximab administration in 195 evaluable patients with muscle weakness due to refractory polymyositis (n=76), dermatomyositis (n=76), or juvenile dermatomyositis (n=48) in the Rituximab in Myositis (RIM) trial. Improvement was defined as at least a 20% improvement in 3 of any 6 core set measures (CSM) plus no more than 2 CSMs worsening by more than 25% (excluding muscle manual testing [MMT]). The 6 CSMs consisted of MMT using the MMT-8 measure, patient global visual analog scale (VAS), physician global VAS, Health Assessment Questionnaire disability index, muscle enzymes, and global extramuscular disease activity score. The time to achieve the preliminary International Myositis Assessment and Clinical Studies Group definition of improvement was 20 weeks in patients who received "early" rituximab (at weeks 0 and 1, followed by placebo at weeks 8 and 9) compared with 20.2 weeks in patients who received "late" rituximab (at weeks 8 and 9, with placebo at weeks 0 and 1). At 8 weeks, 15% of the rituximab group and 20.6% of the placebo group had met the definition of improvement. In 160 patients receiving a mean of 20.8 mg/day of prednisone at baseline, the mean dosage significantly decreased to 14.4 mg/day at the end of the trial. Of the 17 patients with worsening disease after initial improvement, 9 were retreated with rituximab and 8 of these met the definition of improvement after 19.9 weeks. Infections were the most common serious adverse event, particularly pneumonia (n=6) and cellulitis (n=6). Infusion reactions were significantly more common with rituximab than placebo (15.4% vs 5.3%), with 4 severe reactions and 2 hospitalizations. Glucocorticoids were not administered as premedications. Rituximab was administered in adults at a dosage of 750 mg/m2/dose up to 1000 mg/dose IV for 2 doses given 1 week apart. Patients were also receiving stables doses of glucocorticoids and at least one other immunosuppressant.

Support for rituximab as a treatment for systemic sclerosis-associated interstitial lung disease can be found in a guideline and meta-analysis. Hachulla et al indicated rituximab may be considered as a third-line treatment option in patients with systemic sclerosis-associated interstitial lung disease who have failed cyclophosphamide and/or mycophenolate. A meta-analysis by de Figueriredo Caldas et al found rituximab significantly improved lung function, but not skin fibrosis, in adults with systemic sclerosis. A systematic review that included the 3 studies from the meta-analysis (90 patients) plus 7 nonrandomized studies (128 patients) reported mixed results.

Support for using rituximab to treat thyroid eye disease is supported by a European guideline. The European Group on Grave’s orbitopathy (EUGOGO) indicate rituximab may be used as a second-line treatment for moderate to severe and active Graves' orbitopathy of recent onset (less than 12 months) if refractory to IV glucocorticoids, excluding patients with risk for dysthyroid optic neuropathy. This recommendation is based on two small, randomized double-blind, conflicting trials that differ in final treatment dosage.

Support for using rituximab for chronic graft versus host disease (cGVHD) can be found in the National Comprehensive Cancer Network’s guideline for hematopoietic cell transplantation. The NCCN Guideline for hematopoietic cell transplantation supports the use of rituximab as additional therapy in conjunction with systemic corticosteroids following no response (steroid-refractory disease) to first-line therapy options.

Support for using rituximab as conditioning for allogenic transplant can be found in the National Comprehensive Cancer Network's guideline for hematopoietic cell transplantation. The NCCN Guideline for hematopoietic cell transplantation supports the use of rituximab as conditioning for allogenic transplant as part of a non-myeloablative regimen in combination with cyclophosphamide and fludarabine.

Support for using rituximab for the management of immunotherapy-related toxicities can be found in the National Comprehensive Cancer Network's guideline for the management of immunotherapy-related toxicities. The NCCN Guideline for hematopoietic cell transplantation supports the use of rituximab as additional therapy for moderate (G2), severe (G3), or life-threatening (G4) immunotherapy-related bullous dermatitis. The guideline also supports the use of rituximab for moderate, severe, or life-threatening steroid-refractory myositis (proximal muscle weakness, neck flexor weakness, with or without myalgias) for significant dysphagia, life-threatening situations, or cases refractory to corticosteroids. Additionally, rituximab may be used as additional therapy for severe (G3-4) myasthenia gravis in patients refractory to plasmapheresis or intravenous immune globulin (IVIG). Finally, rituximab can be used for encephalitis in patients positive for autoimmune encephalopathy antibody, or who have limited or no improvement after 7 to 14 days on high-dose corticosteroids with or without IVIG.

Support for rituximab as a treatment for neuromyelitis optica spectrum disorder can be found in a randomized trial. Tahara et al found that rituximab compared with placebo significantly reduced the relapse rate in adults with neuromyelitis optica spectrum disorder (NMOSD) who were or had been anti-aquaporin-4 antibody positive (AQP4+). In the 20-month, open-label RIN-2 extension study, relapses were greatly reduced and nearly all patients were completely withdrawn from oral steroids. Rituximab significantly reduced relapses compared with azathioprine in adults (about half AQP4+) in a 12-month randomized trial; more patients discontinued for adverse effects with azathioprine.

Support for rituximab as a treatment for solid organ transplant can be found in guidelines, retrospective studies, and case series. Costanzo et al recommended immune globulin (IVIG) infusion, plasmapheresis, either alone or combined, rituximab, and in very select cases, splenectomy as desensitization therapies for heart transplant. Rituximab may be added to initial therapy (may include immunoadsorption and corticosteroid or plasmapheresis/low dose of IV immunoglobulin and corticosteroid) to reduce the risk of recurrent rejection in heart transplant patients. Chih et al found that rituximab and plasma cell therapies (bortezomib) are the basis of desensitization treatment for heart transplant evidenced by increasing transplantation rates, reduced wait-list time, and graft outcomes similar to non-sensitized patients. Short-term outcomes in patients desensitized with various combinations of rituximab, IVIG, bortezomib, plasmapheresis, and immunoadsorption have been similar to those in patients not receiving desensitization agents. Since rituximab is a human monoclonal antibody and activates complement, it may create false positive crossmatch results. Rituximab and plasma cell depleting therapies (bortezomib) have been used in the treatment of antibody-mediated heart rejection but success rates have been variable. Adjunctive treatment with rituximab and/or bortezomib may be considered. Ravichandran et al found that the addition of rituximab to standard treatment (steroids and plasmapheresis with or without IV immunoglobulin (IVIG)) significantly decreased all-cause mortality and increased survival for 1 week or longer and at 3 years in a small retrospective study in patients with clinical suspicion of rejection following heart transplant. Baradaran et al found that in a case series of patients who underwent liver transplant and developed acute antibody-mediated rejection (AMR) all 4 treated with rituximab survived and had

adequate liver function. Sakamoto et al found that in a case series of patients who underwent liver transplant and developed AMR, half of adult patients treated with rituximab had improvement of liver function without progression of fibrosis while the other half of adults died due to graft failure complicated with sepsis or progression of fibrosis or hepatic necrosis. In a case series case series of patients who underwent liver transplant and developed antibody-mediated rejection (AMR) less than half of pediatric patients treated with rituximab had improvement of liver function and pathological findings, while the remainder of patients had progression of fibrosis, and there was a death due to graft failure. Dhanasekaran et al found that in a case series of patients who underwent liver transplant and developed AMR, half of adult patients treated with rituximab had improvement of liver function without progression of fibrosis while the other half of adults died due to graft failure complicated with sepsis or progression of fibrosis or hepatic necrosis. Anti-B-cell agents (eg, rituximab), IV immunoglobulin, and bortezomib (antiproteasome antibody that depletes plasma cells) have been used in treatment of antibody-mediated liver transplant rejection. Charlton et al found that treatment of moderate to severe antibody-mediated liver transplant rejection may include plasmapheresis and IV immunoglobulin with or without anti-B cell or plasma cell drugs (e.g., rituximab, bortezomib, or eculizumab) Available data are based on case reports or inferred from the strategies used in non-hepatic transplants. Neuhaus et al, Vacha et al, Otani et al, and Witt et al found that Rituximab has been used for the treatment of antibody-mediated rejection (AMR) in adult lung transplant recipients. Vianna et al found that in intestine transplants induction with rabbit antithymocyte globulin plus rituximab compared with less intensive induction significantly reduced the risk of acute cellular rejection (ACR) and severe ACR during the first 24 days posttransplant but not after 24 days and significantly reduced the risk of graft loss due to rejection during the first 6 months posttransplant but not after 6 months. Kubal et al and Vianna et al found that in intestine transplant patients induction with rabbit antithymocyte globulin and rituximab followed by maintenance with tacrolimus and steroids with or without an anti-IL-2 receptor antibody was associated with acute rejection in about a quarter to half of the patients.

Support for rituximab as a treatment for polyarteritis nodosa can be found in a guideline and some case reports. Chung et al indicated that rituximab may be considered in newly diagnosed, active, severe polyarteritis nodosa (defined as vasculitis with life-or organ-threatening disease [e.g., renal disease, mononeuritis multiplex, muscle disease, mesenteric ischemia, coronary involvement, limb/digit ischemia]). Treatment should be initiated with cyclophosphamide and glucocorticoids over rituximab and glucocorticoids. Efficacy remains uncertain. In some case reports, rituximab was successful in the treatment of severe, refractory polyarteritis nodosa but is role remains uncertain due to the lack of comparative or larger single-arm trials.

Support for rituximab as a treatment for membranous nephropathy can be found in guidelines from KDIGO. Rituximab can be considered in those with membranous nephropathy and at least one risk factor for disease progression.

Support for rituximab as a treatment for Susac syndrome can be found in clinical trials and a review of medical literature. Currently, the best treatment for patients with SS is not known. Despite the “belief” that SS is a B cell–mediated disease, patients have been treated with B as well as T cell therapies with success. A review of the literature provides many different paradigms for treatment that include various combinations of drugs: corticosteroids, intravenous immunoglobulin (IVIG), mycophenolate mofetil, azathioprine, methotrexate, cyclophosphamide, and rituximab. If a patient is breaking through on this

initial dual therapy, mycophenolate mofetil and/or rituximab should be added. Rituximab is initiated as a single dose of 500 mg given once and then repeated in 6 months. Some practitioners may give rituximab 250 mg once then repeated in 2 weeks followed by 500 mg every 6 months and some may treat with slightly higher doses.

Support for rituximab as a treatment for non-infectious scleritis can be found in randomized trials. Rituximab was an effective treatment option for refractory non-infectious scleritis, particularly in cases associated with systemic autoimmune diseases including granulomatosis with polyangiitis (GPA) or rheumatoid arthritis (RA). A positive clinical response is typically observed within about 2 months and 88% to 100% of patients achieve remission lasting 14 to 15 months. In a comprehensive review of use of rituximab in non-infectious uveitis and scleritis, rituximab given primarily as a third-line treatment for refractory non-infectious scleritis was associated with a 93.3% response rate with 88.4% experiencing at least a temporary remission.

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