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Policy Number: 046.005

Title: Coverage Determination Policy for Rituximab (Rituxan), Rituximab-abbs (Truxima), Rituximab-pvvr (Ruxience), Rituximab-arrx (Riabni) and Rituximab/Hyaluronidase (Rituxan Hycela) for Non-Oncologic uses

Regions: ☒ **Texas** ☐ **Florida** ☐ **Indiana** ☐ **New Jersey** ☒ **New Mexico**

Impacted Areas:

- ☒ Network Management/Provider Services
- ☐ Member services
- ☐ Quality Management
- ☐ IT
- ☐ Administration
- ☐ Compliance/delegation
- ☒ Utilization Management
- ☐ Case management
- ☐ Disease management
- ☐ Human resources
- ☐ Finance
- ☒ Pharmacy
- ☐ ALL

Available LCD/NCD/LCA: None

Disclaimer:

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Doctors helping patients for more than 25 years

Title: Coverage Determination Policy for Rituximab for Non-Oncologic uses

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Coverage Policy Number: 046.005

Line of Business: Medicare Part B

Policy Type: Prior Authorization

Coverage Determination:

STEP THERAPY CRITERIA

This policy supplements the Medicare guidelines for the purpose of determining coverage under the Part B medical benefits. This Step Therapy Policy is implemented to enforce a step therapy requirement for new starts only. This policy is not applicable to members continuing therapy within the past 365 days. Coverage is granted if Medicare Coverage requirements plus these step criteria are met.

All products for non-oncology uses will require prior authorization		
Truxima (rituximab-abbs)	**Q5115**	**Preferred**
Ruxience (rituximab-pvvr)	**Q5119**	**Preferred**
Rixuxan Hycela (Rituximab and hyaluronidase	J9311	Non-Preferred
Rituxan (rituximab)	J9312	Non-Preferred
Riabni (rituximab-arrx)	Q5123	Non-Preferred

Non-Preferred Step Therapy Criteria

Riabni, **Rituxan**, or **Rituxan Hycela** may be covered when any of the criteria listed below are satisfied:

I. History of use of Ruxience or Truxima resulting in minimal clinical response to therapy and residual disease activity; **or**
II. History of intolerance or adverse event(s) to Ruxience or Truxima; **or**
III. Continuation of prior therapy within the past 365 days.

Initial/New Requests

Please, refer to the National Comprehensive Cancer Network (NCCN) guideline (NCCN templates) for all Oncology indications:

Rituximab/hyaluronidase (Rituxan Hycela): Agent is unproven and not medically necessary for the treatment of non-oncology indications

WellMed Medical Management will cover rituximab (Rituxan), rituximab-abbs (Truxima), Rituximab-pvvr (Ruxience), Rituximab-arrx (Riabni) as medically necessary for **ALL** of the following **non-oncology indications**:

1) Auto-immune hemolytic anemia[24]

2) Immune thrombocytopenic purpura (ITP) when all of the following criteria are met: [20-21]
   I. Documented platelet count < 30 x 10^9 / L ; and
   II. History of failure, contraindication, or intolerance to one of the following:
      a. Anti-D immunoglobulin
      b. Corticosteroids
      c. Immune globulin
      d. Splenectomy
      e. Thrombopoietin receptor agonist (TPO-RA) (e.g., Promacta [eltrombopag], Nplate [romiplostim])

3) Thrombotic thrombocytopenic purpura (TTP) when all of the following criteria are met: [16-18]
   I. In combination with steroids and plasma exchange except when contraindicated, and
   II. One of the following:
      a. Patient is receiving concurrent therapy with glucocorticoids
      b. History of contraindication or intolerance to glucocorticoids

4) Neuromyelitis optica when all of the following criteria are met: [9]
   I. Diagnosis of neuromyelitis optica spectrum disorder (NMOSD) confirming all of the following:
      a. Serologic testing for anti-aquaporin-4 immunoglobulin G (AQP4-IgG)/NMO-IgG antibodies has been performed; and
      b. Past medical history of (if AQP4-IgG/NMO-IgG positive one of the following, if negative two of the following):
         - 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 and
- Serologic testing for anti-aquaporin-4 immunoglobulin G (AQP4-IgG)/NMO-IgG antibodies has been performed; and

c. Diagnosis of multiple sclerosis or other diagnoses have been ruled out; and

d. Patient is not receiving rituximab in combination with any of the following:
- Disease modifying therapies for the treatment of multiple sclerosis [e.g., Gilenya (fingolimod), Tecfidera (dimethyl fumarate), Ocrevus (ocrelizumab), etc.]
- Anti-IL6 therapy [e.g., Actemra (tocilizumab), Kevzara (sarilumab)]
- Complement inhibitors [e.g., Soliris (eculizumab), Ultomiris (ravulizumab)]

5) Post-transplant B-lymphoproliferative disorder (PTLD)

6) Wegener's granulomatosis and Microscopic Polyangiitis (MPA) when the following criteria are met:
   I. Patient is receiving concurrent therapy with glucocorticoids or has a history of contraindication or intolerance to glucocorticoids

7) Microscopic polyarteritis nodosa in combination with glucocorticoids when the following criteria are met:
   I. Patient has not responded to treatment with glucocorticoid and cyclophosphamide after three months of initiation.

8) Moderate to severe Pemphigus Vulgaris (PV) in adult patients when used in combination with a tapering course of glucocorticoids

9) Active rheumatoid arthritis (RA) when all the following criteria are met:
   I. Patient is receiving concurrent therapy with methotrexate or has a history of contraindication or intolerance to methotrexate
   II. Inadequate response, intolerance, or contraindication to at least ONE Tumor Necrosis factor inhibitor (TNF) (i.e., Enbrel, Humira, Remicade)
   III. Patient is not receiving rituximab in combination with either of the following:
      a. Biologic DMARD [e.g., Enbrel (etanercept), Humira (adalimumab), Cimzia (certolizumab), Simponi (golimumab)]
      b. Janus kinase inhibitor [e.g., Xeljanz (tofacitinib)]

10) Immunotherapy-related encephalitis when all of the following criteria are met:
   I. Recent immunotherapy treatment with a checkpoint inhibitor [e.g., Keytruda (pembrolizumab), Opdivo (nivolumab), Tecentriq (atezolizumab)]

II. Inadequate response, history of contraindication or intolerance to glucocorticoids
III. Positive result of autoimmune encephalopathy antibody
IV. Possible infectious causes (e.g., viral) of encephalitis have been ruled out

11) Primary progressive multiple sclerosis (PPMS) or relapsing forms of multiple sclerosis when the following criteria are met:
    I. Patient will not receive rituximab in combination with the following classes of medications
        a. Disease modifying therapy (e.g., interferon beta preparations, dimethyl fumarate, glatiramer acetate, natalizumab, fingolimod, cladribine, siponimod, or teriflunomide)
        b. B cell targeted therapy (e.g., ocrelizumab, belimumab, ofatumumab)
        c. Lymphocyte trafficking blockers (e.g., alemtuzumab, mitoxantrone)
12) Refractory Lupus Nephritis and Systematic Lupus Erythematosis (SLE)

13) Myasthenia Gravis when the following criteria are met:
    I. Patient has MuSK-AB+ MG
    II. Unresponsive to initial immunotherapy:
        a. Corticosteroids and one of the following:
        b. Azathioprine, Cyclophosphamide, cyclosporine, methotrexate, tacrolimus, mycophenylate mofetil, efgartigimod, or ravulizumab

14. Minimal Change Disease use is recommended in frequently relapsing or steroid dependent disease when treatment with high dose glucocorticoids fails.

a. Patient had previous cyclophosphamide
b. Patient wishes to avoid cyclophosphamide treatment [29]

NOTE:

- WellMed Medical Management will NOT cover **rituximab (Rituxan), rituximab-abbs (Truxima), Rituximab-pvvr (Ruxience), Rituximab-arrx (Riabni)** for any indication NOT approved by FDA or supported by evidence-based literature.
- WellMed Medical Management will NOT cover rituximab **(Rituxan), rituximab-abbs (Truxima), Rituximab-pvvr (Ruxience), Rituximab-arrx (Riabni)** for any of the above listed indications for any patient with serious, active infections.

Renewals/Continuation of Therapy Requests

1. Physician documented patient experienced positive clinical response to therapy
2. Dosing is in accordance with (FDA) approved labeling

FDA Approved Indications

FDA Approved Indications**Drug**	**Indication**	**Approved Dosing *(refer to Micromedex for specific regimens if additional dosing information needed)***
Rituxan (rituximab) **Rituximab-abbs (Truxima)** **Rituximab-pvvr (Ruxience)** **Rituximab-arrx (Riabni)**	Auto-immune hemolytic anemia and immune thrombocytopenia	375mg/m2 once a week for 4 weeks
	Wegener's granulomatosis and Microscopic polyarteritis nodosa	In combination with glucocorticoids 375mg/m2 once weekly for 4 weeks. The follow up dose for patients with GPA and MPA who have achieved disease control with induction treatment, in combination with glucocorticoids is two 500 mg intravenous infusions separated by two weeks, followed by a 500 mg intravenous infusion every 6 months thereafter based on clinical evaluation
	Moderate to severe Pemphigus Vulgaris (PV) in adult patients	Two 1000 mg intravenous infusions separated by 2 weeks in combination with a tapering course of glucocorticoids, then a 500 mg intravenous infusion at Month 12 and every 6 months thereafter or based on clinical evaluation. Dose upon relapse is a 1000 mg intravenous infusion with considerations to resume or increase the glucocorticoid dose based on clinical evaluation. Subsequent infusions may be no sooner than 16 weeks after the previous infusion
	Rheumatoid Arthritis	In combination with methotrexate is two 1000 mg intravenous infusions separated by 2 weeks (one course) every 24 weeks or based on clinical evaluation, but not sooner than every 16 weeks.
	Immune thrombocytopenic purpura (ITP)	375mg/m2 IV once weekly for four doses
	Thrombotic thrombocytopenic purpura (TTP)	375mg/m2 IV weekly for 4 doses in combination with standard therapy (steroids and plasma exchange), dosed up to a maximum of 1,225 mg per dose
	Pemphigus vulgaris (Moderate to Severe)	1000 mg intravenous infusions every 2 weeks times 2 doses, followed by maintenance dose of 500 mg every 6 to 12 months based on clinical evaluation
Rituxan (rituximab)	Neuromyelitis optica	375mg/m2 IV weekly for 4 doses, dosed up to a maximum of 1,225 mg per dose then at 6 months and 12 months after with 1000mg every 2 weeks X 2 doses each time[23]
Rituxan (rituximab)	Post-transplant B-lymphoproliferative disorder (PTLD)	375mg/m2 IV weekly for 4 doses, dosed up to a maximum of 1,225 mg per dose[22]

General Background:

Rituximab is a chimeric monoclonal antibody directed against transmembrane CD20 proteins on the surface of immature and mature B lymphocytes. The effect of rituximab binding to these proteins is cell lysis and a reduction in antibody-producing capacity. This results in a lowered autoimmune activity in Rheumatoid arthritis. Infusions of rituximab in patients with Rheumatoid Arthritis have less variability than patients with lymphoma.

Rituxan Hycela is a combination of rituximab, a CD20-directed cytolytic antibody and hyaluronidase human, an endoglycosidase, indicated for the treatment of adult patients with follicular lymphoma, diffuse large B-cell lymphoma and chronic lymphocytic leukemia. Rituxan Hycela can only be initiated after patients have received at least one full dose of a rituximab product by intravenous infusion.

Both products carry a Black Box Warning. Rituxan's Black Box Warning reads as follows: RITUXAN administration can result in serious, including fatal, infusion reactions. Deaths within 24 hours of RITUXAN infusion have occurred. Approximately 80% of fatal infusion reactions occurred in association with the first infusion. Monitor patients closely. Discontinue RITUXAN infusion for severe reactions and provide medical treatment for Grade 3 or 4 infusion reactions. Severe, including fatal, mucocutaneous reactions can occur in patients receiving RITUXAN. HBV reactivation can occur in patients treated with RITUXAN, in some cases resulting in fulminant hepatitis, hepatic failure, and death. Screen all patients for HBV infection before treatment initiation, and monitor patients during and after treatment with RITUXAN. Discontinue RITUXAN and concomitant medications in the event of HBV reactivation. Progressive Multifocal Leukoencephalopathy (PML), including fatal PML, can occur in patients receiving RITUXAN.

Warnings

Fatal infusion-related reactions, mucocutaneous reactions, reactivation of hepatitis B virus (HBV), and progressive multifocal leukoencephalopathy (PML) are some of the black box warning reported. Patient should be screened for HBV infection prior to treatment, monitor and discontinue rituximab infusion after severe reactions.

Clinical Evidence

American College of Rheumatology (ACR)

According to the American College of Rheumatology (ACR) guideline (see table below), it is important that RA patients be seen regularly to assess disease activity, evaluate disease severity, and determine whether alternative therapies are warranted. Because there was no evidence to support a specific recommendation on the frequency of provider visits, a specific and potentially arbitrary time frame is not recommended at this point. However, based on these recommendations, commonly used but not exclusive tools to assess the RA disease activity include: Disease Activity Score (DAS) in 28 joints, Simplified Disease Activity Index (SDAI), Clinical Disease Activity Index (CDAI), Rheumatoid Arthritis Disease Activity Index, Patient Activity Scale (PAS), and Routine Assessment Patient Index Data. In addition, it is recommended to use the combinations of commonly used but not exclusive prognostic factors to evaluate the patients with RA, including: Health Assessment Questionnaire (HAQ) score, Evidence of radiographic erosions, Elevated erythrocyte sedimentation rate, Elevated C-reactive protein level, and elevated levels of rheumatoid factor (RF) and/or anti– cyclic citrullinated peptide (anti-CCP) antibodies. Due to the absence of a single "gold standard" measure, multiple measures or pooled indices are used to determine a diagnosis, estimate prognosis, and to assess and monitor disease activity and response to treatment. Other commonly used measures in the clinical settings include: Visual Analogue scale (VAS), Likert scales of global response to pain by the patient/doctor, and Global Arthritis Score (GAS).

Summary of 2015 American College of Rheumatology (ACR) recommendations for the treatment of Established rheumatoid arthritis (RA). Green and bolded = strong recommendation. A strong recommendation means that the panel was confident that the desirable effects of following the recommendation outweigh the undesirable effects (or vice versa), so the course of action would apply to most patients, and only a small proportion would not want to follow the recommendation. Yellow and italicized = conditional recommendation: The desirable effects of following the recommendation probably outweigh the undesirable effects, so the course of action would apply to the majority of the patients, but some may not want to follow the recommendation. Because of this, conditional recommendations are preference sensitive and always warrant a shared decision-making approach.

The ACR Recommendations for patients with established RA are as follows:

Recommendations for patients with Established RA[1]	Level of Evidence (evidence reviewed)
1. Regardless of disease activity level, use a treat-to-target strategy rather than a non-targeted approach (PICO B.1).	Moderate (44-46)
2. If the disease activity is low, in patients who have never taken a DMARD, use DMARD monotherapy (MTX preferred) over a TNFi (PICO B.2).	Low (47,48)
3. *If the disease activity is moderate or high in patients who have never taken a DMARD:* • *use DMARD monotherapy (MTX preferred) over tofacitinib (PICO B.3).* • *use DMARD monotherapy (MTX preferred) over combination DMARD therapy (PICO B.4).*	*High (49)* *Moderate (18,20-25)*
4. If disease activity remains moderate or high despite DMARD monotherapy, use combination traditional DMARDs or add a TNFi or a non-TNF biologic or tofacitinib (all choices with or without MTX, in no particular order of preference), rather than continuing DMARD monotherapy alone (PICO B.5).	Moderate to Very low (23,26,29,30,47,48,50-59)
5. If disease activity remains moderate or high despite TNFi therapy in patients who are currently not on DMARDs, add one or two DMARDs to TNFi therapy rather than continuing TNFi therapy alone (PICO B.6).	High (60-65)
6. *If disease activity remains moderate or high despite use of a single TNFi:* • *use a non-TNF biologic, with or without MTX, over another TNFi with or without MTX (PICO B.12 and B.14).* • *use a non-TNF biologic, with or without MTX, over tofacitinib with or without MTX (PICO B.13 and B.15).*	*Low to Very low (66-72)* *Very low[4]*
7. *If disease activity remains moderate or high despite use of a single non-TNF biologic, use another non-TNF biologic, with or without MTX, over tofacitinib, with or without MTX (PICO B.16 and B.17).*	*Very low[4]*
8. *If disease activity remains moderate or high despite use of multiple (2+) sequential TNFi therapies, first use a non-TNF biologic, with or without MTX, over another TNFi or tofacitinib (with or without MTX) (PICO B.8, B.9, B.10, B.11).*	*Very low (73-75)*
9. *If the disease activity still remains moderate or high despite the use of multiple TNFi therapies, use tofacitinib, with or without MTX, over another TNFi, with or without MTX, if use of a non-TNF biologic is not an option (PICO B.23 and B.24).*	*Low (29,30)*
10. *If disease activity remains moderate or high despite use of at least one TNFi and at least one non-TNF-biologic:* • *first use another non-TNF biologic, with or without MTX, over tofacitinib (PICO B.21 and B.22).* • *If disease activity remains moderate or high, use tofacitinib, with or without MTX, over another TNFi (PICO B.19 and B.20).*	*Very low (29,30)* *Very low (29)*
11. *If disease activity remains moderate or high despite use of DMARD, TNFi, or non-TNF biologic therapy, add short-term, low dose glucocorticoid therapy (PICO B.26 and B.27).*	*High to Moderate (33,41,76,77)*
12. *If disease flares in patients on DMARD, TNFi, or non-TNF biologic therapy, add short-term glucocorticoids at the lowest possible dose and the shortest possible duration (PICO B.28 and B.29).*	*Very low (40-43)*
13. *If the patient is in remission:* • *taper DMARD therapy (PICO B.31)[2].* • *taper TNFi, non-TNF biologic, or tofacitinib (PICO B.33, B.35, B.37) (please also see #15).*	*Low[3] (78)* *Moderate to Very low[3] (79,80)*
14. If disease activity is low: • continue DMARD therapy (PICO B.30). • continue TNFi, non-TNF biologic or tofacitinib rather than discontinuing respective medication (PICO B.32, B.34 and B.36).	Moderate (78) High to Very low (79,80)
15. If the patient's disease is in remission, do not discontinue all RA therapies (PICO B.38).	Very low[4]

A treatment recommendation favoring one medication over another means that the preferred medication would be the recommended first option and the nonpreferred medication may be the second option. Favoring one medication over the other does not imply that the nonfavored medication is contraindicated for use; it is still an option. Therapies are listed alphabetically; azathioprine, gold, and cyclosporine were considered but not included. Disease-modifying antirheumatic drugs (DMARDs) include hydroxychloroquine, leflunomide, methotrexate (MTX), and sulfasalazine. 1 = definition of established RA is based on the 1987 ACR RA classification criteria, since the 2010 ACR/European League Against Rheumatism RA classification allows classification of a much earlier disease state. 2 = tapering means scaling back therapy (reducing dose or dosing frequency), not discontinuing it. Tapering should be considered an option and not be mandated. If done, tapering must be conducted slowly and carefully, watching for increased disease activity and flares. Even for patients whose RA is in remission, there is some risk of flare when tapering. 3 = evidence is rated low quality or moderate to very low quality because some evidence reviewed for this recommendation was indirect and included studies with discontinuation rather than tapering of therapy or since studies involved patients achieving low disease activity rather than remission. 4 = no studies were available, leading to very low quality evidence, and the recommendation was based on clinical experience.

In a Multicenter, Randomized, Double-blind, Placebo-Controlled, Phase III trial, Cohen et. al evaluated the efficacy of treatment with rituximab plus methotrexate in patients with active rheumatoid arthritis who were enrolled in the Randomized Evaluation of long term efficacy of rituximab in RA (REFLEX) trial. Patients with active RA and an inadequate response to 1 or more

anti-TNF agents were randomized to receive IV rituximab (N=311) or placebo (N= 209), both with background MTX. The primary endpoint for efficacy was a response on the American College of Rheumatology 20% improvement criteria (ACR20) at 24 weeks. Secondary efficacy endpoints were responses on ACR50 and ACR70 improvement criteria, and the European League against Rheumatism (EULAR) response criteria at 24 weeks. At 24 weeks, significantly more patients in the rituximab treatment arm had ACR20 (51% in rituximab arm versus 18% in placebo arm; p<0.0001), ACR50 (27% in rituximab arm versus 5% in placebo arm; p<0.0001), and ACR70 (12% in rituximab arm versus 1% in placebo arm; p<0.0001) responses. The rituximab arm also demonstrated significantly more patients with moderate to good EULAR responses compared to the placebo arm (65% vs. 22%, P<0.0001). The rituximab-treated patients also had clinically significant improvements in fatigue, disability, and health-related quality of life.

Smolen et. al reviewed several published literature include meta-analysis and randomized controlled trials that evaluated the efficacy of rituximab in treating patients with rheumatoid arthritis. As a result of their findings, the investigators recommended the use of rituximab for the treatment of active RA (at least moderate disease activity) in patients with inadequate response to (or intolerance of) Tumor Necrosis Factor (TNF) inhibitors.

Expert opinions have suggested the use of rituximab in the treatment of auto-immune hemolytic anemia and immune thrombocytopenia, but as of date no randomized clinical trials have been done. One systemic review by Arnold at el found that the use of rituximab resulted in an increase in overall platelet count in adults with ITP. However, the result was derived from uncontrolled studies, which also reported significant toxicities including death. Another randomized trial investigated efficacy of rituximab in combination with dexamethasone in the treatment of adult patients with immune thrombocytopenia purpura (ITP). Again, the results suggest that rituximab in combination with dexamethasone improved platelet counts and thus patient outcomes without compromising patient's safety, when compared with dexamethasone alone. The authors suggest that this combination could be an option for second-line treatment in patients unresponsive to steroids and as an alternative prior to splenectomy.

A retrospective, multicenter analysis conducted by Mealy M et.al compared the relapse and treatment failure rates among 90 patients receiving azathioprine, mycophenolate mofetil and rituximab for Neuromyelitis optica at the Mayo clinic and John Hopkins Hospital during the past 10 years. Comparative analysis results showed up to 88.2% reduction in the relapse rate up in patients taking rituximab versus 87.4% relapse rate reduction with mycophenolate mofetil versus 72.1 % reduction in relapse rate with azathioprine. The investigators concluded that initial treatment with rituximab significantly reduces relapse rates in Neuromyelitis optica and Neuromyelitis Optica spectrum disorder patients.

KDIGO 2021

The pathogenesis of MCD is unclear, but evidence supports T cell dysregulation driving the podocytopathy. The effectiveness of B cell–depleting therapeutic agents also suggests a role for B cells in disease pathogenesis. In general, adult MCD is similar to SSNS in children. However, response to glucocorticoid treatment is slower in adults than children. We recommend high-dose oral glucocorticoids for initial treatment of MCD. Rituximab is effective in observational

studies of FR/SD MCD in patients needing glucocorticoids with or without other maintenance immunosuppressive therapies. Overall, the efficacy of rituximab in inducing remission is between 65% and 100%, and notably, it is associated with a reduction in the number of relapses and a reduction in the number of immunosuppressive medications. However, experience with rituximab is limited, and the long-term efficacy/risks in this population are unknown. [30]

Algorithm for the initial treatment of MCD in adults

Medication	Regimen	Remission rates (complete and partial)
Initial episode, glucocorticoid treatment		
Prednisone or prednisolone	Dose: 1 mg/kg per day (maximum 80 mg/day) or 2 mg/kg every other day (maximum 120 mg every other day), for a minimum of 4 weeks, and a maximum of 16 weeks (as tolerated). After remission, taper over at least 24 weeks	80%–90%
Initial episode with contraindication to glucocorticoids		
Oral cyclophosphamide	2–2.5 mg/kg per day for 8 weeks	75%
Cyclosporine	3–5 mg/kg per day in divided doses for 1–2 years	75%
Tacrolimus	0.05–0.1 mg/kg per day in divided doses for 1–2 years	90%*
Frequently relapsing/ steroid-dependent patients		
Oral cyclophosphamide	2–2.5 mg/kg/day, adjusted for white blood counts, for 8–12 weeks. 12 weeks may be associated with less relapse in steroid-dependent MCD	75%
Calcineurin inhibitors • Cyclosporine • Tacrolimus	**Initial dose:** 3–5 mg/kg per day in divided doses for 1–2 years 0.05–0.1 mg/kg per day in divided doses for 1–2 years • If serum levels are being monitored, suggested initial levels: - Cyclosporine: 150–200 ng/ml (125–166 nmol/l) - Tacrolimus: 4–7 ng/ml (5–8.7 nmol/l) • After withdrawal of glucocorticoids reduce CNI dose if possible Suggested doses: <3mg/kg/day for cyclosporine and <0.05 mg/kg/day for tacrolimus • Attempt gradual taper and discontinuation of CNI after a minimum of one year of therapy if possible • If CNI-dependent reduce dose to lowest possible to maintain remission with monitoring of kidney function (kidney biopsy if kidney dysfunction) Switch to alternate medication if evidence of CNI toxicity	70%–90% 90%
Rituximab	**Induction regimens:** • 375 mg/m² weekly for 4 doses • 375 mg/m² × single dose; repeat after one week if CD19 cells >5/mm³ • 1 g/dose for 2 doses, 2 weeks apart **Relapse after induction:** • 375 mg/m² × 1 dose or • 1g i.v. × 1 dose	70% (20% off all immunosuppression, 50% on one other immunosuppressive drug)
Mycophenolic acid analogues • Mycophenolate mofetil • Sodium mycophenolate	**Initial dose:** 1000 mg twice daily 720 mg twice daily • Attempt gradual taper and discontinuation of mycophenolic acid analogues after a minimum of one year of therapy if possible	

Frontiers in Immunology

Recently, RTX has been introduced as an induction drug for LN, and studies suggested that RTX seemed to be at least as effective as MMF and CYC regimens in inducing remission. Still, few studies were conducted to compare the efficacy and safety of RTX with common therapeutic drugs, especially TAC.

In the present study, the numbers of CR, PR, and overall responses were considered as efficacy outcomes. In terms of CR, RTX showed a significantly higher CR than MMF (OR = 2.60, 95% CrI = 1.00–7.10) and seemed to be more effective than CYC (OR = 4.20, 95% CrI = 1.70–14.00) Similarly, MMF had a better CR than CYC (OR = 1.60, 95% CrI = 1.00–3.20). Regarding overall

response, TAC presented a better overall response than CYC (OR = 3.70, 95% CrI = 1.20–12.00). As for PR, no significant differences were found among the four drugs

Table 4 presents the SUCRA values (%) for treatment efficacy and safety of each regimen. Regarding CR, the maximum SUCRA value of RTX was 96.94%, suggesting that RTX was likely to achieve the highest CR among these four treatment drugs. In terms of overall response, the maximum SUCRA value of TAC was 80.15%, meaning that TAC had the highest overall response among these four drugs. Besides, CYC was likely to achieve the highest PR among drugs, as it presented a higher probability of PR (SUCRA = 69.47%). As for safety, ranking probability based on SUCRA suggested that TAC was the safest treatment, as its minimum SUCRA value was 30.17%.

Table 4

Rank probability of efficacy and safety for each treatment drug.

Treatments	Complete remission	Partial remission	Total remission	Infection
RTX	96.94	35.29	73.57	74.98
TAC	49.86	62.72	80.15	30.17
MMF	48.34	32.53	40.47	45.71
CYC	4.87	69.47	5.81	49.14

CYC, cyclophosphamide; RCT, randomized controlled trial; RTX, rituximab; TAC, tacrolimus.

RTX was the most effective drug for inducing CR among LN patients, followed by TAC and MMF. CYC was the most successful medicine for inducing PR among patients with LN, followed by TAC and RTX. In terms of overall response, TAC was the most effective treatment drug for achieving overall response among LN patients, followed by RTX and MMF. As for safety, TAC was the safest treatment with the lowest likelihood of infection events. However, RTX showed the highest probability of experiencing infection without considering other adverse events.

In summary, RTX and TAC were the most effective drugs for inducing remission among LN patients, and TAC had the lowest probability of infection compared with the other drugs [27]

International Consensus Guidance for Management of Myasthenia Gravis

Most studies of RTX are retrospective, and some combine patients with AChR-Ab, MuSK-Ab, and seronegative MG. A multicenter blinded prospective review of MuSK-Ab + MG patients demonstrated that 14 of 24 (58%) patients treated with RTX achieved MM status and required only low-dose IS therapy, compared with 5 of 31 (16%) of the non-RTX group.[19]

In a prospective open-label study of 22 refractory AChR-Ab+, MuSK-Ab+, and seronegative MG, MG manual muscle testing (MMT) scores revealed significant improvement from baseline at a mean follow-up of 29 ± 19 months in the AChR-Ab+ and MuSK-Ab+ groups. Another prospective open-label study of 14 patients with refractory AChR-Ab+, MuSK-Ab+, and seronegative MG reported improvement in MMT scores at a mean follow-up of 22 months. The time to peak response after a single cycle of RTX was 4.5 ± 1 months. A retrospective multicenter study of MuSK-Ab + MG reported that RTX given in the dose of 375 mg/m^2 weekly for 4 weeks and then monthly for the next 2 months was associated with lower relapse rates (18%) compared with a regimen of two 1 g infusions separated by 2 weeks (80%). A retrospective Austrian nationwide study of 56 patients with AChR-Ab+ and MuSK-Ab + MG reported that 26% of patients were in remission 3 months after treatment with varying dosing protocols of RTX. At a median of 20 months, 43% were in remission and 25% achieved MM status. A single-center retrospective study of 21 AChR-Ab+, 3 MuSK-Ab+, and 4 patients with double-seronegative MG found that muscle strength improved significantly from baseline at 6 months and then stabilized up to 36 months, and PIS was improved in 43% at 6 months.[24] A retrospective combined analysis of previously published case reports of 169 patients between January 2000 and August 2015 reported that 72% of MuSK-Ab + MG and 30% of AChR-Ab+ MG patients treated with RTX achieved MM status or better.

Rituximab should be considered as an early therapeutic option in patients with MuSK-Ab+ MG who have an unsatisfactory response to initial immunotherapy (median 9, range 4–9). The efficacy of RTX in refractory AChR-Ab+ MG is uncertain. It is an option if patients fail or do not tolerate other IS agents (median 8, range 4–9) [28]

HCPCS Code

HCPCS Code:	Description:
J9312	**Rituximab (Rituxan)**
Q5115	**Rituximab-abbs (Truxima)**
Q5119	**Rituximab-pvvr (Ruxience)**
Q5123	**Rituximab-arrx (Riabni)**

Acronyms

TNF – tumor necrosis factor, RA- Rheumatoid Arthritis, **ACR** – American College of Rheumatology, **NCD** – National Coverage Determination, **LCD** – Local Coverage Determination, **FDA** – Food and Drug Administration, **PV** – Pemphigus Vulgaris, **MTX** – methotrexate, **DAS** - Disease Activity Score (DAS), **SDAI** - Simplified Disease Activity Index, **CDAI** - Clinical Disease Activity Index, **PAS** - Patient Activity Scale, **HAQ** - Health Assessment Questionnaire, **RF** - rheumatoid factor, **anti-CCP** - anti–cyclic citrullinated peptide, **GAS** - Global Arthritis Score, **PICO** - population, intervention, comparator, and outcomes, **TNFi** = tumor necrosis factor inhibitor

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