AETNA BETTER HEALTH®

Clinical Policy Bulletin:
Rituximab (Rituxan)

Number: 0314

Policy

I. Aetna considers rituximab (Rituxan) medically necessary for any of the following indications:

A. Acute lymphoid leukemia (induction/consolidation therapy for Philadelphia chromosome-negative ALL for patients aged greater than or equal to 40 years); or

B. Anti-neutrophil cytoplasmic antibody-associated (ANCA-associated) vasculitides (Wegener granulomatosis, Churg-Strauss syndrome, microscopic polyangiitis, and pauci-immune glomerulonephritis) in persons with an inadequate response to cyclophosphamide; or

C. Antibody mediated rejection in heart transplant recipients, prevention of recurrence; or

D. CD20-positive chronic lymphocytic leukemia; or

E. Chronic graft versus host disease (last resort treatment); or

F. Corticosteroid-refractory autoimmune blistering diseases (pemphigus vulgaris, pemphigus foliaceus, bullous pemphigoid, cicatricial pemphigoid, epidermolysis bullosa acquisita and paraneoplastic pemphigus); or

G. Cryoglobulinemia refractory to corticosteroids and other immunosuppressive agents; or

H. In combination with methotrexate to reduce signs and symptoms and to slow the progression of structural damage in adult members with moderately-to-severely active rheumatoid arthritis who have had an inadequate response to 2 or more tumor necrosis factor (TNF) antagonist therapies (see note); or

I. Lymphocyte-predominant Hodgkins lymphoma; or

J. Multi-centric Castleman's disease (angiofollicular lymph node hyperplasia); or

K. Non-Hodgkin's lymphoma; or

L. Opsoclonus-myoclonus-ataxia associated with neuroblastoma, that is refractory to steroids, chemotherapy and intravenous immunoglobulins; or

M. Post-transplant lymphoproliferative disorder; or

N. Prophylaxis of rejection in sensitized kidney transplant recipients with donor specific antibodies; or

O. Refractory autoimmune hemolytic anemia; or

P. Relapsed or refractory hairy cell leukemia in persons who have failed at multiple (2 or more) courses of cladribine; or

Q. Sjogren syndrome refractory to corticosteroids and other immunosuppressive agents; or

R. Treatment of neuromyelitis optica when one or more immunotherapies have failed; or

S. Treatment of factor inhibitors in persons with hemophilia; or

T. Treatment of refractory immune or idiopathic thrombotic thrombocytopenic purpura, refractory thrombotic thrombocytopenic purpura; or

U. Waldenström's macroglobulinemia.

The efficacy of more than 2 courses of infusions (each course may entail 4 to 8 weekly infusion) for non-Hodgkins lymphoma in 48 weeks is unknown.

II. Note: This note applies to the use or rituximab for rheumatoid arthritis: There are several brands of targeted immune modulators on the market. There is a lack of reliable evidence that any one
brand of targeted immune modulator is superior to other brands for medically necessary indications. Enbrel (etanercept), Humira (adalimumab), Remicade (infliximab), Simponi Aria (golimumumab intravenous) and Stelara (ustekinumab) brands of targeted immune modulators ("least cost brands of targeted immune modulators") are less costly to Aetna. Consequently, because other brands (e.g., Actemra (tocilizumab), Cimzia (certolizumab), Cosentyx (secukinumab), Entyvio (vedolizumab), Kineret (anakinra), Orencia (abatacept), Otezla (apremilast), Rituxan (rituximab), Simponi (golimumab), and Xeljanz (tofacitinib)) of injectables are more costly than these least cost brands of targeted immune modulators, and least cost brands of targeted immune modulators are at least as likely to produce equivalent therapeutic results, no other brands of targeted immune modulator will be considered medically necessary unless the member has a contraindication, intolerance or incomplete response to at least 2 of the least cost brands of targeted immune modulator: Enbrel, Humira, Remicade, Simponi Aria or Stelara, for the same medically necessary indication. If the least costly targeted immune modulator does not have the labeled indication (see appendix), then Aetna considers medically necessary another brand of targeted immune modulator that has the required labeling indication. For some Aetna plans, the use of other brands of intravenously infused targeted immune modulators (tocilizumab (Actemra), abatacept (Orencia), and rituximab (Rituxan)) will not be considered medically necessary unless the member has a contraindication, intolerance or incomplete response to the least cost brand of intravenously infused targeted immune modulator, infliximab (Remicade) for the same medically necessary indication.

III. Aetna considers rituximab experimental and investigational for all other indications because its effectiveness for these indications has not been established, including (not an all-inclusive list):

- Acute disseminated encephalomyelitis
- Acute myeloid leukemia
- Anti-myelin-associated glycoprotein neuropathy
- Anti-phospholipid syndrome
- Arthritis associatae with inflammatory bowel disease
- Autoimmune encephalitis (e.g., limbic autoimmune encephalitis, NMDA-receptor antibody encephalitis)
- Autoimmune neutropenia
- Autoimmune pancreatitis/atrophy of the pancreas
- Autoimmune polyendocrine syndrome type 1 (APS-1) [also known as autoimmune polyendocrinopathy candidiasis and ectodermal Ddsplasia (APECED)]
- Autoimmune retinopathy
- Behcet's disease
- Bile salt export pump deficiency after liver transplantation
- Birdshot retinochoroidopathy
- Bronchiolitis obliterans
- Cerebral folate deficiency
- Chronic inflammatory demyelinating polyneuropathy (CIDP)/IgM-associated polyneuropathy
- Cogan's syndrome
- Complex regional pain syndrome (reflex sympathetic dystrophy)
- Dermatomyositis
- GALOP syndrome (Gait disorder_ataxia; Autoantibodies_IgM against central myelin antigen; Late age of Onset; Polyneuropathy)
- Goodpasture's syndrome
- Granulomatous lymphocytic interstitial lung disease (GLILD)
- Graves ophthalmopathy
- Hashimoto's encephalitis
- Hemophagocytic lymphohistiocytosis
- Idiopathic nephrotic syndrome
- Idiopathic pulmonary fibrosis
- Immune complex vasculitis
- IgG4 related sclerosing disease
- Juvenile dermatomyositis
- Juvenile rheumatoid arthritis (juvenile idiopathic arthritis)
- Kawasaki disease
IV. Aetna considers anti-chimeric antibody testing and/or chimeric anti-TNF antibody testing for rituximab therapy experimental and investigational because of insufficient evidence in the peer-reviewed literature.

Background

Non-Hodgkin’s lymphoma (NHL) is a cancer of the lymphatic tissue causing enlargement of lymph nodes and generalized symptoms (Wake et al, 2002). It is a heterogeneous condition. Follicular lymphoma behaves in an indolent fashion, with a median survival of 8 to 12 years. However, it is incurable and most patients with the disease will die from it.

According to the literature, management of NHL consists of intermittent treatment when the disease relapses and causes symptoms. The aim is to maximize quality of life by inducing remission, abolishing the symptoms associated with relapse, with minimal treatment side-effects. Cancer-specific treatment is not usually instituted while the patient is asymptomatic ("watchful waiting"). According to available guidelines, first-line therapy of NHL is usually oral chlorambucil (or an equivalent alkylating agent). Second-line treatment is usually an anthracycline-containing chemotherapy regime.

Rituximab is a genetically engineered chimeric mouse/human monoclonal antibody directed against the CD20 antigen found on the surface of normal and malignant B lymphocytes. It is given as an
intravenous infusion once-weekly for 4 doses (days 1, 8, 15, and 22). Rituximab represents a novel approach to treatment of low-grade NHL, targeting malignant cells without the adverse effects associated with chemotherapy. A pivotal study (Linch, 2001) has demonstrated a response rate of 56% in relapsed or refractory low-grade NHL.

The U.S. Pharmacopoeial Convention (2003) has concluded that rituximab (Rituxan) is accepted for the following off-label indications: a) as first-line treatment of diffuse aggressive NHL; b) treatment of relapsed or refractory diffuse aggressive NHL; c) first-line treatment of intermediate to high-grade NHL; and d) first-line treatment of low-grade NHL.

The U.S. Pharmacopoeial Convention (2002) has concluded that rituximab is also effective for second-line treatment of patients with relapsed or refractory CD20 positive chronic lymphocytic leukemia (CLL). Chronic lymphocytic leukaemia is essentially the bloodstream form of NHL, and is the most common type of leukemia. The disease usually progresses slowly and many people with chronic lymphocytic leukemia (CLL) do not need treatment for months or years. Chronic lymphocytic leukemia mainly affects older people and is rare in people under age 40.

Published evidence from Phase I and Phase II trials have shown that rituximab has activity against CLL with acceptable toxicity. Perry and Rasool (2001) stated that “[t]herapy with monoclonal antibodies has been evaluated in patients with CLL. The most useful agent in clinical trials so far appears to be CAMPATH-1H, an antibody directed at CD52. Rituxan (rituximab) also is effective as a second-line or third-line treatment and may assume a more prominent role in the future.” The National Cancer Institute's PDQ on Chronic Lymphocytic Leukemia (January 2002) states that "CAMPATH-1H and rituximab (monoclonal antibodies) are under clinical evaluation. Higher doses of rituximab than those used for other non- Hodgkin lymphomas are required.”

An April 2001 Cancer Care Ontario Evidence Review of rituximab, however, concluded that "[t]he response rates reported for CLL/SLL continue to be lower than for other histologies and appear lower than those reported for other agents used in this disease.” A Toronto Regional Cancer Centre Guideline for CLL (2001) states that "When used in routine doses/scheduling, the chimeric anti-CD20 monoclonal antibody rituximab has been disappointing in the management of CLL.”


There are several published phase II studies of rituximab for lymphocyte predominance Hodgkin's disease (LPHD) (Younes et al, 2003; Ekstrand et al, 2003; Rehwald et al, 2003). Additional studies of rituximab for LPHD are currently ongoing. Younes et al (2003) examined the potential role of infiltrating benign B cells in classic HD lesions in supporting the survival of malignant Hodgkin and Reed-Sternberg (H/RS) cells. The authors initiated a pilot study of rituximab, which is used to primarily deplete normal B cells from HD lesions. Patients with recurrent, classic HD who had received a minimum of 2 prior treatment regimens, regardless of whether H/RS cells expressed CD20, were treated with 6 weekly doses of 375 mg/m2 rituximab to selectively deplete infiltrating benign B cells. Objective tumor response was determined 3 weeks after completion of the last dose of rituximab and every 3 months thereafter. Serum samples were collected from patients before they started rituximab therapy and 3 weeks after the final course of rituximab. Serum cytokine levels of interleukin 6 (IL-6), IL-10, IL-12, IL-13, and interferon gamma were determined using commercially available enzyme-linked immunosorbent assay kits. Twenty-two patients with nodular sclerosis histology were evaluable for treatment response. Five patients (22%) achieved partial or complete remission that lasted for a median of 7.8 months (range of 3.3 to 14.9 months). Remissions were observed in patients only at lymph node and splenic sites, but not at extra-nodal sites, and were irrespective of CD20 expression by H/RS cells. Furthermore, systemic (B) symptoms resolved in 6 of 7 patients after therapy. In 2 patients, partial remissions were associated with a decline in serum IL-6 levels. The authors concluded that current data suggest that rituximab therapy in patients with recurrent, classic HD can alter serum IL-6 cytokine levels, can improve B symptoms, and may result in clinical remissions.
Ekstrand et al (2003) stated that LPHD is a unique clinical entity characterized by indolent nodal disease that tends to relapse after standard radiotherapy or chemotherapy. The malignant cells of LPHD are CD20+ and therefore rituximab may have activity with fewer late effects than standard therapy. In this phase 2 trial, 22 patients with CD20+ LPHD received 4 weekly doses of rituximab at 375 mg/m2. Ten patients had previously been treated for Hodgkin disease, while 12 patients had untreated disease. All 22 patients responded to rituximab (overall response rate, 100 %) with complete response (CR) in 9 (41 %), unconfirmed complete response in 1 (5 %), and partial response in 12 (54 %). Acute treatment-related adverse events were minimal. With a median follow-up of 13 months, 9 patients had relapsed, and estimated median freedom from progression was 10.2 months. Progressive disease was biopsied in 5 patients: 3 had recurrent LPHD, while 2 patients had transformation to large-cell non-Hodgkin lymphoma (LCL). All 3 patients with recurrent LPHD were retreated with rituximab, with a second CR seen in 1 patient and stable disease in 2. Rituximab induced prompt tumor reduction in each of 22 LPHD patients with minimal acute toxicity; however, based on the relatively short response duration seen in the trial and the concerns about transformation, rituximab should be considered investigational treatment for LPHD. Further clinical trials are needed to determine the optimal dosing schedule of rituximab, the potential for combination treatment, and the possible relationship of rituximab treatment to the development of LCL.

In a phase 2 study, Rehwald et al (2003) evaluated the safety and efficacy of rituximab in patients with relapsed LPHD or other CD20(+) subtypes of Hodgkin disease (HD). Eligibility criteria required expression of the CD20 antigen on more than 30 % of malignant cells. A total of 14 patients were treated with 4 weekly intravenous infusions of rituximab (375 mg/m2). All patients had at least 1 prior chemotherapy (median, 2). The median time from first diagnosis was 9 years. Adverse events, such as rhinitis, fever, chills, and nausea, were usually transient and of mild to moderate grade, allowing outpatient treatment in most cases. All patients completed treatment and were eligible for a response. The overall response in 14 assessable patients was 86 %, with 8 complete remissions and 4 partial remissions, and 2 patients with progressive disease. At a median follow-up of 12 months, 9 of 12 responders were in remission. The median duration of response has not been reached yet (20+ months). The authors concluded that rituximab is both safe and effective in a subgroup of CD20(+) patients with HD.

The U.S. Pharmacopeial Convention has concluded that rituximab is indicated for treatment of Waldenström’s macroglobulinemia. Dimopolous et al (2002) reported on 27 patients with symptomatic Waldenström’s macroglobulinemia who were treated with rituximab. Twelve patients (44 %; 95 % confidence interval [CI]: 25.5 % to 64.7 %) achieved a partial response after treatment with rituximab. Median time to response was 3.3 months (range of 2.2 to 7.1 months). The median time to progression for all patients was 16 months, and with a median follow-up of 15.7 months, 9 of 12 responding patients remain free of progression. The investigators reported that approximately 25 % of patients experienced some mild form of infusion-related toxicity, usually fever and chills. The U.S. Pharmacopoeial Convention has also concluded that rituximab is indicated for treatment of idiopathic thrombocytopenic purpura. This conclusion is based on the results of several single-institution cohort studies that have reported on response rates exceeding 50 %, and only minor adverse events. Stasi et al (2001) stated that “[i]n view of its mild toxicity and the lack of effective alternative treatments, its use in the setting of chronic refractory ITP is warranted.”

Rituximab may be considered for persons with relapsed or refractory hairy cell leukemia who have failed at least two courses of cladribine. The National Cancer Institute information on hairy cell leukemia (NCI, 2007) states that rituximab can be used for relapsed or refractory hairy cell leukemia after failure of purine analog therapy (i.e., cladribine). “Rituximab can induce durable complete remissions with minimal toxic effects in the majority of patients with relapsing or refractory disease after purine analog therapy. The lack of subsequent immunosuppression with rituximab has made this treatment the first choice among relapsing patients in the absence of a clinical trial.” The largest clinical trial of rituximab for hairy cell leukemia reported to date (Nieva et al, 2003) reported that rituximab “has only modest single-agent activity in cladribine-failed HCL patients when compared with other agents active in this disease.”

Rituximab has been approved for use in rheumatoid arthritis. An assessment of targeted immune modulators by the Drug Evaluation Research Project (DERP0 (Thaler, et al., 2012) found insufficient evidence to reach conclusions of the comparative efficacy of rituximab with other targeted immune modulators, because of heterogeneity of studies.
Edwards et al (2004) reported on the results of an multi-center randomized controlled clinical trial of rituximab in rheumatoid arthritis, which found that a single course of 2 infusions of rituximab alone or in combination provided significant improvement in disease symptoms for 48 weeks. The investigators randomly assigned 161 adults who had active rheumatoid arthritis despite treatment with methotrexate to receive 1 of 4 treatments: oral methotrexate; rituximab; rituximab plus cyclophosphamide; or rituximab plus methotrexate. Eligible patients had active disease despite treatment with at least 10 mg of methotrexate per week. Active disease was defined by the presence of at least 8 swollen and 8 tender joints and at least 2 of the following: a serum C-reactive protein level of at least 15 mg per liter, an erythrocyte sedimentation rate of at least 28 mm per hour, or morning stiffness lasting longer than 45 minutes. In addition, eligible patients were seropositive for rheumatoid factor. At 24 weeks, the proportion of patients with 50 % improvement in disease symptoms according to American College of Rheumatology (ACR) criteria, the primary end point, was significantly greater with the rituximab-methotrexate combination (43 %, p = 0.005) and the rituximab-cyclophosphamide combination (41 %, p = 0.005) than with methotrexate alone (13 %). In all groups treated with rituximab, a significantly higher proportion of patients had a 20 % improvement in disease symptoms according to the ACR criteria (65 to 76 % versus 38 %, p < 0.025) or had EULAR responses (83 to 85 % versus 50 %, p < 0.004). All ACR responses were maintained at week 48 in the rituximab-methotrexate group. The investigators reported that the majority of adverse events occurred with the first rituximab infusion. At 24 weeks, serious infections occurred in one patient (2.5 %) in the control group and in 4 patients (3.3 %) in the rituximab groups. Peripheral-blood immunoglobulin concentrations remained within normal ranges. The investigators concluded that in patients with active rheumatoid arthritis despite methotrexate treatment, a single course of 2 infusions of rituximab, alone or in combination with either cyclophosphamide or continued methotrexate, provided significant improvement in diseases symptoms at both 24 and 48 weeks.

Rituximab has been investigated for use in a number of other indications, including thrombotic thrombocytopenic purpura, cryoglobulinemia, chronic inflammatory polyneuropathy, multiple myeloma, and idiopathic autoimmune hemolytic anemia.

Rituximab has been investigated for use in thrombotic thrombocytopenic purpura. However, current evidence is limited to case reports and small case series (Yomtovian et al, 2004).

A number of reports have indicated the usefulness of rituximab in the treatment of subjects with warm agglutinin autoimmune hemolytic anemia not responding to conventional treatment including corticosteroids and splenectomy (Zecca et al, 2001; D'Arena et al, 2006; Gupta et al, 2002; Shanafelt et al, 2003; Mantadakis et al, 2004) and to cold agglutinin disease not responding to conventional treatments (Schollkopf et al, 2006; Berentsen et al, 2004).

Rituximab has also been investigated in the treatment of cryoglobulinemia (e.g., Zaja et al, 2003; Sansonno et al, 2003; Arzoo et al, 2002; Barociani et al, 2002). However, controlled studies are needed to better define the value of rituximab for this indication (Zaja et al, 2003). Consensus Panel Recommendations from the Second International Workshop on Waldenström’s Macroglobulinemia (Gertz et al, 2003) did not list rituximab among effective interventions for symptomatic mixed cryoglobulinemia (MC).

A Cochrane systematic evidence review (Hughes et al, 2003) concluded that there is inadequate evidence of the effectiveness of rituximab in the treatment of chronic inflammatory polyneuropathy.

An uncontrolled, 3-month study of rituximab in 19 subjects with multiple myeloma has shown promising results in a subgroup of subjects who expressed CD20 on their bone marrow plasma cells (Treon et al, 2002).

Two randomized, controlled clinical trials found rituximab to be non-inferior to cyclophosphamide-containing regimens in the induction of remission in persons with ANCA-associated vasculitis. In the RAVE trial (Stone et al, 2010), investigators compared intravenous rituximab and oral cyclophosphamide in 197 patients. The investigators found rituximab to be non-inferior to cyclophosphamide, with 64 % in the rituximab group reaching the primary end point of remission without need for prednisone at 6-month follow-up, compared with 53 % of the cyclophosphamide group. In the 101 patients with relapsing disease, rituximab was significantly more effective.
The European Vasculitis Study group (Jones et al, 2010) compared 4 weeks of intravenous rituximab plus 2 doses of cyclophosphamide to intravenous cyclophosphamide followed by azathioprine in patients with ANCA-associated renal vasculitis. Of 44 patients, 76% of rituximab recipients and 82% of cyclophosphamide recipients experienced the primary end point of sustained remission at 12 months. Rates of adverse effects were similar in both groups; 18% of patients in each group died.

These findings are consistent with an earlier case series report (Eriksson et al, 2005), which reported the results of rituximab treatment 2 women with refractory myeloperoxidase-ANCA-positive microscopic polyangiitis and 7 patients (5 men and 2 women) with refractory proteinase 3-ANCA-positive Wegener's granulomatosis. All patients were resistant to conventional therapy or had relapsed repeatedly after cessation of cyclophosphamide (Cyc). The cases were treated with intravenous infusions of rituximab once a week 2 times (3 cases) or 4 times (6 cases). To prevent formation of antibodies to rituximab, mycophenolate mofetil (5 patients), azathioprine (1 patient), or a short course of Cyc (2 patients) were added or allowed to continue. Main outcome measures were remission at 6 months assessed with Birmingham vasculitis activity score. The cases were followed 6 to 24 months and relapse rate was also noted. Eight of 9 patients responded completely and 1 case responded partially. Pulmonary X-ray improved (4 cases), progress of lower extremity gangrene stopped (1 case), remission of neuropathy was stable (1 patient), renal vasculitis went into remission (2 cases), and severe musculoskeletal pain improved (1 case). Minor relapse in the nose occurred in 2 cases. No adverse events or major infections were noted.

In an open-label uncontrolled pilot study (n = 7), Levine (2005) reported their findings of 7 adult patients with dermatomyositis (DM), 6 of whom had longstanding illness that was responding inadequately to a number of currently available immunosuppressive agents. All patients received 4 intravenous infusions of rituximab given at weekly intervals. Patients were followed up for up to 1 year without further treatment with rituximab. One patient was lost to follow-up. The principal effectiveness outcome was muscle strength, measured by quantitative dynamometry. All 6 evaluable patients exhibited major clinical improvement, with muscle strength increasing over baseline by 36 to 113%. Maximal improvements in muscle strength occurred as early as 12 weeks after the initial infusion of rituximab. CD20+ B cells were effectively depleted in all patients by 12 weeks. Four patients experienced a return of symptoms that coincided with the return of B cells before the 52-week end point. Two patients maintained their increased muscle strength at 52 weeks, and 1 of these patients maintained this strength even after the return of B cells. Other symptoms of DM (e.g., rash, alopecia, and reduced forced vital capacity) improved markedly in patients with these symptoms. Rituximab was well-tolerated, with no treatment-related severe or serious adverse events during the observation period of this study. The authors concluded that the results of this small open-label study of DM patients treated with rituximab provided sufficiently encouraging results to justify a more formal evaluation of the value of B cell depletion therapy in the treatment of DM. Furthermore, in a review on “B cell-targeted therapy in diseases other than rheumatoid arthritis”, Looney (2005) stated that “depletion of B cells during rituximab therapy was associated with improvement in global disease activity …. further controlled studies are warranted to optimize rituximab as monotherapy and to develop combination therapies in patients with refractory autoimmune diseases”.

In an open-label study, Mok and colleagues (2007) reported the effectiveness and toxicity of rituximab in the treatment of refractory polymyositis. Adult patients with active polymyositis as evidenced by persistent proximal muscle weakness, elevated creatine kinase (CK) level, and features of active myositis on electromyography who were refractory to corticosteroids and at least 2 other immunosuppressive agents were recruited. While immunosuppressive agents were continued, rituximab (375 mg/m2) was given by intravenous infusion weekly for 4 consecutive weeks. Patients were followed-up 4-weekly for serial assessment of muscle power, serum muscle enzymes, physician's and patient's global impression of disease activity, disability, and quality of life scores. Four patients (3 women, 1 man) were studied. The mean age was 53 +/- 11 years and the mean duration of polymyositis was 4.8 +/- 3.3 years. All had persistently active myositis for at least 2 years. At Week 28, significant improvement in the mean proximal muscle power scores and reduction in CK levels in comparison to baseline were observed. Two patients had return of full muscle power with significant drop in CK level. There was a trend of improvement in disability scores as well as both the mental and physical components of the Medical Outcomes Study Short Form-36 Health Survey scores. Rituximab was well-tolerated. The authors concluded that rituximab is an option to be considered in refractory polymyositis, however, further controlled trials are needed to confirm its effectiveness.
There is evidence for the effectiveness of rituximab for post-transplant lymphoproliferative disorders (PTLD) (Cincinnati Hospital Children's Medical Center, 2003). PTLD is a life-threatening complication following solid organ transplantation. Treatment with rituximab, a humanized anti-CD20 monoclonal antibody, has proved to be a promising approach and shown a low toxicity profile. Oertel et al (2005) reported on the results of a multi-center phase II trial investigating rituximab as single agent in 17 patients with PTLD. Transplanted organs were heart (n = 5), kidney (n = 4), lung (n = 4) and liver (n = 4). Patients were treated with 4 weekly doses of 375 mg/m(2) of rituximab. The mean follow-up time was 24.2 months. The investigators reported that rituximab therapy was well-tolerated and no severe adverse events were observed. The mean overall survival period is 37.0 months with 11 patients still living at the time of the report. In total, 9 patients (52.9%) achieved a complete remission, with a mean duration of 17.8 months. Partial remission was observed in 1 patient, minor remission in 2 patients, no change in 3 patients and 1 patient experienced progressive disease. Two patients relapsed, at intervals 3 and 5 months after obtaining complete remission. The investigators concluded that rituximab proved to be well-tolerated and effective in the treatment of PTLD.

There is emerging evidence for the effectiveness of rituximab in Castleman's disease (CD). Two clinical classifications of CD have been described: unicentric (unifocal or localized) and multi-centric (multifocal or generalized) (Dispenzieri and Gertz, 2005). The uni-centric presentation responds well to surgical resection and is associated with a benign course. The multi-centric presentation requires systemic therapy and prognosis is guarded. Associated systemic symptoms are common. There is an increased incidence of CD in patients with HIV. The human herpes virus-8 is associated with nearly all of the HIV-associated CD cases and nearly 50 % of non-HIV cases. Interleukin (IL)-6 has also been shown to play a significant role in the pathogenesis of the disease. Paraneoplastic and autoimmune entities are not uncommon in the disorder. Variable benefit has been achieved with rituximab (Dispenzieri and Gertz, 2005; Ide et al, 2006; Casquero et al, 2006; Marcelin et al, 2003). Patients with CD are at increased risk for developing frank malignant lymphoma.

Ahmed and Wong (2007) noted that mixed cryoglobulinemia (CG) is a systemic immune complex-mediated disease that involves small-to-medium vessel vasculitis, provoked by the CG containing immune complexes that precipitate in cold. It is associated with hepatitis C virus (HCV) infection in 80 % of patients. Mixed CG-mediated vasculitis can affect the kidney, liver and heart. Laboratory parameters show presence of cryoglobulin, and in most cases of mixed CG, rheumatoid factor IgM kappa. The current treatment strategy of HCV-associated CG includes targeting the viral trigger HCV with a combination of anti-viral medication, interferon-alpha and ribavirin, or the downstream pathogenic events by means of plasmapheresis, steroids or immunosuppression. With multi-organ involvement, the anti-viral therapy may be limited due to severity of renal disease, treatment failure, side effects or contraindications. On the other hand, immunosuppressive therapy may be poorly tolerated or ineffective. Thus, new treatment options such as rituximab have been proposed as a rescue therapy. These researchers reviewed the literature to evaluate the current evidence in treating HCV-related refractory mixed CG. There have been many published case series and case reports on the use of rituximab in the treatment of HCV-related CG. However, there has been no randomized controlled trial. In the literature, there have been 60 patients with CG treated with rituximab. The male to female ratio was 14:46. A total of 53 patients were HCV-positive; 46 had mixed type II CG, 7 had type III CG, and for 7 the type was not specified. Twenty-five patients had renal involvement ranging from proteinuria, to nephrotic syndrome, to nephritic syndrome, to chronic kidney disease. Eight patients had had a renal transplant and were on immunosuppression. Most patients responded to rituximab, with only 17 of 60 patients relapsing, and 8 of 17 of those were re-challenged with rituximab with a good response. Total follow-up period varied between 3 and 31 months. The authors concluded that rituximab is a suitable rescue therapy in refractory CG associated with HCV. There is evidence supporting the use of rituximab as first-line therapy, as opposed to the proposals of others who would strongly recommend anti-viral therapy. However, a prospective, randomized, controlled trial is needed to assess the safety and effectiveness of rituximab compared with current standard therapy, which includes anti-viral therapy, immunosuppression, as well as plasmapheresis.

More than 80 % of individuals with multiple sclerosis (MS) experience a relapsing-remitting disease course (He et a., 2013). Approximately 10 years after disease onset, an estimated 50 % of individuals with relapsing-remitting MS (RRMS) convert to secondary progressive MS. Multiple sclerosis causes a major socioeconomic burden for the individual patient and for society. Effective treatment that reduces relapse frequency and prevents progression could impact both costs and quality of life and help to reduce the socioeconomic burden of MS. Alternative and more effective MS treatments with new modes
of action and good safety are needed to expand the current treatment repertoire. It has been shown that B lymphocytes are involved in the pathophysiology of MS and rituximab lyses B-cells via complement-dependent cytotoxicity and antibody-dependent cellular cytotoxicity. Current clinical trials are evaluating the role of rituximab as a B-cell depletion therapy in the treatment of RRMS.

He et al (2013) completed an update of the Cochrane review of rituximab for RRMS. The safety and effectiveness of rituximab, as monotherapy or combination therapy, versus placebo or approved disease-modifying drugs (DMDs) (interferon-β (IFN-β), glatiramer acetate, natalizumab, mitoxantrone, fingolimod, teriflunomide, dimethyl fumarate, alemtuzumab) to reduce disease activity for people with RRMS were assessed. The Trials Search Co-ordinator searched the Cochrane Multiple Sclerosis and Rare Diseases of the Central Nervous System Group Specialised Register. The authors checked the references in identified trials and manually searched the reports (2004 to August 2013) from neurological associations and MS societies in Europe and America. They also communicated with researchers who were participating in trials on rituximab and contacted Genentech, Biogen Idec and Roche. The systematic review included all randomised, double-blind, controlled parallel group clinical trials with a length of follow-up equal to or greater than 1 year evaluating rituximab, as monotherapy or combination therapy, versus placebo or approved DMDs for patients with RRMS without restrictions regarding dosage, administration frequency and duration of treatment. The authors used the standard methodological procedures of The Cochrane Collaboration. Two review authors independently assessed trial quality and extracted data. Disagreements were discussed and resolved by consensus among the review authors. Principal investigators of included studies were contacted for additional data or confirmation of data. One trial involving 104 adult RRMS patients with an entry score less than or equal to 5.0 on the Expanded Disability Status Scale (EDSS) and at least 1 relapse during the preceding year was included. This trial evaluated rituximab as monotherapy versus placebo, with a single course of 1,000 mg intravenous rituximab (on day 1 and day 15). A significant attrition bias was found at week 48 (24.0 %). Patients receiving rituximab had a significant reduction in total number of gadolinium-enhancing lesions at week 24 (mean number 0.5 versus 5.5; relative reduction 91 %) and in annualised rate of relapse at week 24 (0.37 versus 0.84) but not at week 48 (0.37 versus 0.72). Disability progression was not included as an outcome in this trial. More patients in the rituximab group had adverse events within the 24 hours after the first infusion (78.3 % versus 40.0 %), such as chills, headache, nausea, pyrexia, pruritus, fatigue, throat irritation, pharyngolaryngeal pain, and most were mild-to-moderate events (92.6 %). The most common infection-associated adverse events (greater than 10 % in the rituximab group) were nasopharyngitis, upper respiratory tract infections, urinary tract infections and sinusitis. Among them, only urinary tract infections (14.5 % versus 8.6 %) and sinusitis (13.0 % versus 8.6 %) were more common in the rituximab group. One ongoing trial was identified. The authors concluded that there is not sufficient evidence to support the use of rituximab as a disease-modifying therapy for RRMS because only 1 randomized controlled trial (RCT) was included. The quality of the study was limited due to high attrition bias, the small number of participants, and short follow-up. The authors concluded that the beneficial effects of rituximab for RRMS remain inconclusive. However, short-term treatment with a single course of rituximab was safe for most patients with RRMS. Mild-to-moderate infusion-associated adverse events were common, as well as nasopharyngitis, upper respiratory tract infections, urinary tract infections and sinusitis. The potential benefits of rituximab for treating RRMS need to be evaluated in large-scale studies that are of high quality along with long-term safety.

In a phase II, double-blind, 48-week clinical trial involving 104 patients with relapsing-remitting multiple sclerosis, Hauser et al (2008) assigned 69 patients to receive 1,000 mg of intravenous rituximab and 35 patients to receive placebo on days 1 and 15. The primary end point was the total count of gadolinium-enhancing lesions detected on magnetic resonance imaging scans of the brain at weeks 12, 16, 20, and 24. Clinical outcomes included safety, the proportion of patients who had relapses, and the annualized rate of relapse. As compared with patients who received placebo, patients who received rituximab had reduced counts of total gadolinium-enhancing lesions at weeks 12, 16, 20, and 24 (p < 0.001) and of total new gadolinium-enhancing lesions over the same period (p < 0.001); and these results were sustained for 48 weeks (p < 0.001). As compared with patients in the placebo group, the proportion of patients in the rituximab group with relapses was significantly reduced at week 24 (14.5 % versus 34.3 %, p = 0.02) and week 48 (20.3 % versus 40.0 %, p = 0.04). More patients in the rituximab group than in the placebo group had adverse events within 24 hours after the first infusion, most of which were mild-to-moderate events; after the second infusion, the numbers of events were similar in the 2 groups. The authors concluded that a single course of rituximab reduced inflammatory brain lesions and clinical relapses for 48 weeks. However, the authors noted that this phase II study was not designed to evaluate long-term safety or to detect uncommon adverse events. They stated that the safety and effectiveness
of rituximab for the treatment of multiple sclerosis need to be validated by larger and longer-term controlled studies. MacFarland (2008) noted that a phase II clinical trial leaves many questions unanswered including the duration of the treatment effect, the effect of progression of disability, and most importantly the types of adverse events that may occur at low frequency. Issues of long-term safety of rituximab must still be addressed, given reports to the FDA of progressive multi-focal leukoencephalopathy in patients with lupus who were treated with rituximab.

Genentech, Inc. (South San Francisco, CA) reported that a Phase II/III randomized, double-blind, placebo-controlled, multi-center study to evaluate the efficacy, safety and tolerability of 4 courses of rituximab for primary-progressive multiple sclerosis (PPMS) did not meet its primary endpoint as measured by the time to confirmed disease progression during the 96-week treatment period. A total of 439 patients were randomized 2:1 to receive either 4 treatment courses of rituximab 6 months apart or placebo. MRI evaluations were conducted at baseline, weeks 6, 48, 96 and 122. The incidence of overall adverse events was comparable between rituximab and placebo treatment groups. Serious adverse events were 16.4% in the rituximab arm versus 13.6% in the placebo arm, with an incidence of serious infections of 4.5% compared with less than 1.0% respectively. Infectious events (10%) reported in either group included upper respiratory and urinary tract infections. Most infectious events in the rituximab arm were reported as mild to moderate in severity, though events of greater severity were reported more frequently in patients receiving rituximab. There were more infusion-related reactions with rituximab, the majority of which were mild to moderate in severity (Genentech, 2008).

A randomized controlled trial (Hawker et al., 2009) of rituximab for PPMS found no significant difference between rituximab and placebo in time to confirmed disease progression, the primary study endpoint. Subgroup analysis suggested that rituximab may have a significant effect on time to confirmed disease progression in younger patients; however, this finding would need to be confirmed in clinical trials designed to test this hypothesis. In an accompanying editorial, Hartung and Aktas (2009) stated that "having failed to reach the primary endpoint, rituximab joins the league of drugs that showed disappointing or inconclusive results in therapy trials in PPMS". Regarding the findings of the subgroup analysis, Hartung and Aktas (2009) commented that "[t]hus, these results suggest that, before jumping to conclusions, a note of caution needs to be added to these types of subgroup analyses. They are of a purely exploratory character and definitely should not guide therapeutic decisions in current neurological practice. However, they do offer important insights into the pathobiology of the disease as correctly pointed out by Hawker and colleagues in their discussion of the findings obtained".

Current evidence regarding the use of rituximab for systemic lupus erythematosus (SLE) is limited. A systematic evidence review and metaanalysis by Borba et al (2014) of biologic therapies for SLE found that rituximab showed no superiority over placebo in terms of efficacy, despite an acceptable safety profile.

In an open study, Leandro et al (2005) reported their findings of 24 patients with severe SLE treated with rituximab and followed for a minimum of 3 months. In the majority of patients (19 out of 24), 6 months follow-up data were described. The authors concluded that for patients who had failed conventional immunosuppressive therapy, considerable utility in the use of B-cell depletion has been demonstrated. They noted that the data obtained in this open study provided strong support for the performance of a full double-blind control trial. This is in agreement with the observation of Sfikakis et al (2005) who stated that double-blind studies comparing rituximab with existing immunosuppressive therapies are needed.

Guidelines from the European League Against Rheumatism (EULAR, 2008) stated that in the absence of randomized controlled clinical trials, rituximab is recommended for selected patients with disease refractory to standard treatments with mycophenolate mofetil and cyclophosphamide. Established treatments for SLE include corticosteroids and the immunosuppressives cyclophosphamide and azathioprine. There is some evidence that oral mycophenolate may be an effective alternative to cyclophosphamide treatment in patients with lupus nephritis.

A study of rituximab for SLE (Ng et al., 2007) examined its efficacy in combination with cyclophosphamide and glucocorticoids in 90 patients with systemic lupus erythematosus refractory to conventional treatment. Following rituximab infusion patients were followed for from 3 to 40 months; a "meaningful" decrease in disease activity was noted in 80%, infusions were well-tolerated in 90% of patients, but adverse events (ascribed to hypersensitivity to the chimeric antibody) occurred in 10%.

In December 2006, the FDA learned that 2 patients who were treated with rituximab for systemic lupus erythematosus developed progressive multifocal leukoencephalopathy (PML), a fatal viral infection of the
central nervous system (FDA, 2007). This side effect has been reported in patients as late as 12 months after their last dose of rituximab. The FDA stated that SLE is not an approved indication for rituximab. A black box warning was added to the labeling of rituximab stating that JC virus infection resulting in PML and death has been reported in patients treated with rituximab.

Genentech, Inc. reported that the EXPLORER study, a phase II/III randomized, double-blind, placebo-controlled, multi-center study of rituximab for SLE, did not meet its primary endpoint defined as the proportion of rituximab treated patients who achieved a major clinical response or partial clinical response measured by BILAG, a lupus activity response index, compared to placebo at 52 weeks. A total of 257 patients were randomized 2:1 to receive rituximab plus prednisone or placebo plus prednisone in 2 infusions 15 days apart. Patients were retreated 6 months later with the same regimen. Patients were evaluated for efficacy every four weeks for 52 weeks. The majority of patients are being monitored to week 78. The study also did not meet any of the 6 secondary endpoints, including: time adjusted area-under-the-curve minus baseline of BILAG score over 52 weeks; proportion of patients who achieve a major clinical response, and proportion of patients who achieve a partial clinical response (including major clinical response) at week 52; proportion of patients who achieve BILAG C or better in all domains at week 24; time to moderate or severe flare over 52 weeks; change in SLE Expanded Health Survey physical function score from baseline at week 52; and proportion of subjects who achieve a major clinical response with 10 mg prednisone per day from weeks 24 to 52 (Genentech, 2008; Merrill, et al., 2010).

Rovin et al (2012) evaluated the efficacy and safety of rituximab in a randomized, double-blind, placebo-controlled phase III trial in patients with lupus nephritis treated concomitantly with mycophenolate mofetil (MMF) and corticosteroids. Patients (n = 144) with class III or class IV lupus nephritis were randomized 1:1 to receive rituximab (1,000 mg) or placebo on days 1, 15, 168, and 182. The primary end-point was renal response status at week 52. Rituximab depleted peripheral CD19+ B cells in 71 of 72 patients. The overall (complete and partial) renal response rates were 45.8 % among the 72 patients receiving placebo and 56.9 % among the 72 patients receiving rituximab (p = 0.18); partial responses accounted for most of the difference. The primary end-point (superior response rate with rituximab) was not achieved. Eight placebo-treated patients and no rituximab-treated patients required cyclophosphamide rescue therapy through week 52. Statistically significant improvements in serum complement C3, C4, and anti-double-stranded DNA (anti-dsDNA) levels were observed among patients treated with rituximab. In both treatment groups, a reduction in anti-dsDNA levels greater than the median reduction was associated with reduced proteinuria. The rates of serious adverse events, including infections, were similar in both groups. Neutropenia, leukopenia, and hypotension occurred more frequently in the rituximab group. The authors concluded that, although rituximab therapy led to more responders and greater reductions in anti-dsDNA and C3/C4 levels, it did not improve clinical outcomes after 1 year of treatment. The authors also found that the combination of rituximab with MMF and corticosteroids did not result in any new or unexpected safety signals.

The FDA-approved labeling for Rituxan includes black box warnings about fatal infusion reactions with rituximab. The labeling states that rituximab administration can result in serious, including fatal reactions, and that deaths within 24 hours of infusion have occurred. The labeling states that approximately 80 % of fatal infusion reactions occurred in association with the first infusion. The labeling states that patients should be carefully monitored during infusion, and that rituximab infusions should be discontinued and medical treatment provided for grade 3 or 4 infusion reactions.

The FDA-approved labeling for Rituxan also includes a black box warning about tumor lysis syndrome (TLS). The labeling states that acute renal failure requiring dialysis with instances of fatal outcome can occur in the setting of TLS following treatment of NHL patients with rituximab.

The labeling also includes black box warnings about severe, including fatal, mucocutaneous reactions in patients receiving rituximab treatment. The labeling warns that JC virus infection resulting in PML and death has been reported in patients treated with rituximab.

Interest in rituximab for minimal change disease is based upon the hypothesis that the disease has an underlying immune mediated basis. Peters et al (2008) stated that minimal change nephrotic syndrome (MCNS) and focal segmental glomerulosclerosis (FSGS) are the main causes of the idiopathic nephrotic syndrome. The former usually responds to steroids and the long-term prognosis is generally good. However, some patients require prolonged treatment with immunosuppressive agents. The latter generally follows a less favorable course: patients do not always respond to steroids and may progress
to end-stage renal disease. Recurrence of FSGS after renal transplantation is frequently observed and may result in graft loss. Recently, anecdotal case reports have described long-term resolution of nephrotic syndrome due to MCNS or FSGS after treatment with rituximab. These investigators presented 4 patients with nephrotic syndrome due to MCNS, FSGS or recurrence of FSGS following kidney transplantation, who were treated with rituximab with variable success. A review of the recent literature suggests that anti-CD20 antibodies may be a promising therapy, especially for patients with MCNS or idiopathic FSGS. The authors concluded that controlled studies are needed to determine the effectiveness of rituximab and to define which patients will benefit. Furthermore, in a review of treatment of MCNS in adults, Meyrier (2009) stated that despite these preliminary exciting results, these findings cannot yet lead to treatment recommendations.

In a review on nephrotic syndrome and rituximab, Haffner and Fischer (2009) noted that rituximab (RTX) has recently gained attention as a potentially successful therapy for complicated idiopathic nephrotic syndrome in children. A number of case reports and 1 prospective non-controlled multi-center trial point to the beneficial effects of RTX as a rescue therapy in children with steroid/cyclosporine-dependent or steroid/cyclosporine-resistant nephrotic syndrome. However, publication bias often results in positive outcomes being more likely to be reported than negative ones and, in particular, the safety profile of this drug in this group of patients remains unclear. The authors concluded that controlled randomized studies are needed to assess this issue, to develop treatment guidelines, to evaluate the therapeutic and economical efficacy, and to define criteria for the selection of patients.

In a review of treatment of nephrotic syndrome in children, Niaudet (2009) commented that "However, both the efficacy and safety of this drug in this group of patients remain unclear. Further studies including controlled trials are needed to determine whether there is a role for RTX in the treatment of children with steroid dependent NS". The author commented that "It is too early to recommend such therapy [rituximab] in children with SRNS [steroid-resistant nephrotic syndrome].

The development of human anti-chimeric antibodies (HACA) against rituximab may have potential clinical consequences (e.g., reduced duration of response to treatment, and requirements for higher doses or more frequent dosing intervals). However, the full clinical impact of HACA is unknown. Leandro and Edwards (2009) noted that the clinical significance of HACA development in patients with rheumatoid arthritis is unclear. Furthermore, FDA-approved labeling for Rituxan does not include recommendation for HACA testing.

Gartlehner and associates (2008) noted that biologics are an important therapeutic option for treating patients with juvenile idiopathic arthritis (JIA). In adults, they are associated with rare but severe adverse events such as serious infections and malignancies. These investigators reviewed systematically the evidence on the safety and effectiveness of biologics for the treatment of JIA. They searched electronic databases up to August 2006. They limited evidence to prospective studies for effectiveness but included retrospective observational evidence for safety. Outcomes of interest were clinical response, radiographical progression, quality of life, and adverse events. One randomized controlled trial (RCT) and 11 uncontrolled prospective studies provided data on effectiveness; 3 additional studies assessed safety. The only RCT and 6 uncontrolled trials support the general effectiveness of etanercept for the treatment of JIA. Internal and external validity of these studies were limited. The evidence on other biologic agents such as adalimumab, abatacept, anakinra, infliximab, rituximab, and tocilizumab was sparse or entirely missing. Because of the lack of sound long-term safety data, evidence is insufficient to draw firm conclusions about the balance of risks and benefits of any biologic agent for the treatment of JIA. Clinicians have to be aware of the lack of evidence supporting a long-term net benefit when considering biologics for patients with JIA.

In a multi-center, retrospective descriptive case series, Eleftheriou et al (2009) reported the safety and effectiveness of biologic therapies in children with primary systemic vasculitis (PSV). Primary retrospective outcome assessment measures were: daily corticosteroid dose; Birmingham Vasculitis Activity Score (BVAS); and adverse events (including infection rate). A total of 25 patients median age 8.8 (range of 2.4 to 16) years; 11 males with active PSV (n = 6 with anti-neutrophil cytoplasmic antibody associated vasculitides, n = 11 with polyarteritis nodosa, n = 7 with unclassified vasculitis, and n = 1 with Behçet's disease) were treated with biologic agents including infliximab (n = 7), rituximab (n = 6), etanercept (n = 4), adalimumab (n = 1) or multiple biologics sequentially (n = 7). Overall, there was a significant reduction in BVAS from a median of 8.5 (range of 5 to 32) at start of therapy to 4 (range of 0 to 19) at median 32 months follow-up (p = 0.003) accompanied by significant reduction in median daily prednisolone requirement from 1 (range of 0.2 to 2) to 0.25 (range of 0 to 1) mg/kg/day, p = 0.000. For
Rituximab (Rituxan) had been increasingly used in autoimmune blistering dermatoses, mainly in pemphigus. Joly et al. (2007) stated that a single cycle of rituximab is an effective treatment for pemphigus vulgaris of pemphigus foliaceus. The investigators studied 21 patients with pemphigus vulgaris or pemphigus foliaceus whose disease had not responded to an 8-week course of 1.5 mg of prednisone per kilogram of body weight per day (corticosteroid-refractory disease), who had had at least 2 relapses despite doses of prednisone higher than 20 mg per day (corticosteroid-dependent disease), or who had severe contraindications to corticosteroids. Patients were treated with 4 weekly infusions of 375 mg of rituximab per square meter of body-surface area. Eighteen of 21 patients had a complete remission at 3 months after the end of treatment. In 8 of the 18 patients, this remission was maintained without corticosteroid or immunosuppressive therapy after a median follow-up of almost 3 years. One patient developed pyelonephritis and another died of septicemia. The investigators concluded that a single cycle of rituximab is an effective treatment for pemphigus (Joly et al., 2007). The investigators warned that, because of its potentially severe side effects, its use should be limited to the most severe types of the disease. An editorialist noted that this study demonstrated the value of a multi-center approach to accomplish relevant clinical research in orphan diseases such as pemphigus (Diaz, 2007).

Kasperkiewicz et al. (2011) concluded that adjuvant rituximab is effective and well-tolerated not only in patients with pemphigus but also with pemphigoid. A total of 17 patients with refractory autoimmune blistering dermatoses (pemphigus vulgaris, n = 8; pemphigus foliaceus, n = 2; bullous pemphigoid, n = 2; mucous membrane pemphigoid, n = 5) were treated 4 times with rituximab at weekly or bi-weekly intervals. Six of 8 patients with a relapse after this regimen received rituximab again twice in a 2-week interval. The investigators reported that all lesions cleared in 14 patients (7 pemphigus vulgaris, 2 pemphigus foliaceus, 2 bullous pemphigoid, 3 mucous membrane pemphigoid), whereas partial healing was found in 3 others (1 pemphigus vulgaris, 2 mucous membrane pemphigoid). Relapses occurred in 8 patients (5 pemphigus vulgaris, 2 pemphigus foliaceus, 1 bullous pemphigoid). Re-treatment with rituximab again resulted in complete (2 pemphigus vulgaris, 1 pemphigus foliaceus, 1 bullous pemphigoid) or partial (2 pemphigus vulgaris) remission.

Peterson and Chan (2009) performed a survey of 71 consecutive patients with autoimmune blistering diseases treated with rituximab from initial use up to 2007, using the PubMed database. The authors stated that a heterogeneous group of patients, including 51 patients with pemphigus vulgaris, 1 with...
Rituximab (Rituxan) treatment, all 6 patients in the control group had OCP progression and became blind in both eyes. Moreover, the authors stated that clinical observation is necessary to study potential long-term adverse effects.

In a retrospective, comparative, interventional case series, Foster et al (2010) compared the safety and effectiveness of the combination therapy of rituximab (RTX) and intravenous immunoglobulin (IVIG) to other immunosuppressive regimens in the treatment of ocular cicatricial pemphigoid (OCP; n = 12). These investigators reviewed medical records of 12 patients with OCP. Ten of the 12 patients were blind in 1 eye after initial systemic immunosuppressive therapies (phase I treatment). Patients were then divided into 2 groups based on treatments received during phase II. The study group consisted of 6 patients who received the combination of RTX and IVIG during phase II of their treatment. For comparison purposes, the control group consisted of 6 patients who during phase II of their treatment received more aggressive immunosuppressive therapies, but not RTX and IVIG. Main outcome measures included blindness (best-corrected visual acuity [BCVA] less than or equal to 20/200) and OCP staging (Foster). The median total follow-up periods were 57.5 and 55.5 months in the control group and the study group, respectively. After phase I treatment, all 6 patients in the control group were blind in 1 eye. Similarly, 4 of the patients in the study group were blind in 1 eye, whereas 2 had good BCVA bilaterally but experienced persistent conjunctival inflammation despite phase I treatment. After phase II treatment, all 6 patients in the control group had OCP progression and became blind in both eyes. In contrast, BCVA was stable and no further progression of OCP staging was observed in all 6 patients in the study group. In the study group, the median follow-up from completion of the RTX and IVIG treatment protocol was 11 months. No adverse events, immediate or delayed, were reported in any of the patients who received the combination therapy of RTX and IVIG. The authors concluded that in this preliminary study, the combination therapy of RTX and IVIG arrested disease progression and prevented total blindness in patients with recalcitrant OCP. They noted that a larger cohort of patients' needs to be studied before definitive conclusions can be made.

Pranzatelli et al (2010) reported the findings of 12 immunotherapy-naïve children with opsoclonus-myoclonus syndrome (OMS) and cerebrospinal fluid (CSF) B cell expansion who received rituximab, adrenocorticotropic hormone (ACTH), and intravenous immunoglobulin. Motor severity lessened 73 % by 6 months and 81 % at 1 year (p < 0.0001). Opsoclonus and action myoclonus disappeared rapidly, whereas gait ataxia and some other motor components improved more slowly. Dosage of ACTH was tapered by 87 %. Reduction in total CSF B cells was profound at 6 months (-93 %). By study end, peripheral B cells returned to 53 % of baseline and serum IgM levels to 63 %. Overall clinical response trailed peripheral B cell and IgM depletion, but improvement continued after their levels recovered. All but 1 non-ambulatory subject became ambulatory without additional chemotherapy; 2 relapsed and remitted; 4 had rituximab-related or possibly related adverse events; and 2 had low-titer human anti-chimeric antibody. The authors concluded that combination of rituximab with conventional agents as initial therapy was effective and safe. They stated that a controlled trial with long-term safety monitoring is indicated.

cavaillhes et al (2009) note that epidermolysis bullosa acquisita (EBA) is a rare autoimmune sub-epidermal blistering disease; it is potentially serious and is often refractory to conventional treatments, including corticosteroids. The authors reported a new case of successful treatment of EBA using rituximab without relapse after 1 year of follow-up. A 76-year-old man was seen for blisters of the skin and mucosa, atrophic scars and milia on areas of friction. The diagnosis of EBA was made on the basis of histological and immunohistochemical criteria. The patient was unsuccessfully treated with topical steroids, dapsone, topical tacrolimus, systemic steroids, mycophenolate mofetil, doxycycline and methotrexate. Four weekly infusions of rituximab of 375 mg/m(2) body area were performed, combined with systemic steroids: they proved beneficial within 3 weeks, with a noticeable improvement and no further blisters at 7 months. After 1 year of follow-up, the skin disease is still stable with 5 mg/day of prednisone alone being given. The authors concluded that this was the 8th reported case of treatment of EBA with rituximab and the 6th successful therapeutic outcome, with good steroid sparing effect and undeniable improvement in quality of life within several months and good tolerability at 12 months of follow-up. This treatment may be proposed early in cases of EBA refractory to conventional treatments. Moreover, the authors stated that clinical observation is necessary to study potential long-term adverse effects.

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Gorman et al (2010) stated that OMS is a severe autoimmune central nervous system disorder, which predominantly affects young children and causes lifelong neurological disability. Early recognition and treatment may yield better outcomes. Appreciation of the spectrum of clinical presentations of OMS, awareness of common mis-diagnoses, and utilization of diagnostic criteria may facilitate the timely diagnosis of OMS. Approximately 50% of patients have an associated neuroblastoma, which may escape detection by traditional methods and require MRI or computed tomography of the torso for diagnosis. In non-paraneoplastic cases, many associated infections have been reported. Although there has been progress in autoantibody identification and CSF B cell expansion is a common finding, there is no diagnostic biomarker for OMS currently. Approximately 80% of reported patients, typically treated with conventional therapies such as ACTH, corticosteroids, and/or intravenous immunoglobulin, develop long-term neurological morbidity. Newer treatment approaches using early, aggressive therapy with cyclophosphamide or rituximab are promising. The authors concluded that the diagnosis of OMS requires a high level of suspicion and a systematic approach for diagnostic testing, particularly for neuroblastoma. They stated that future collaborative studies are needed to determine if early, aggressive therapy will improve the typically poor long-term neurological outcome.

In a retrospective, interventional case series study, Khanna et al (2010) examined the effectiveness of rituximab in patients with refractory Graves' orbitopathy (GO). In a prospective, open-label, interventional clinical trial, Silkiss et al (2010) evaluated the safety and effectiveness of rituximab-mediated B-lymphocyte depletion as treatment for thyroid eye disease (TED; n = 12). Patients with CAS (VISA [vision, inflammation, strabismus and appearance/exposure] classification) of 4 or greater were followed for 1 year after rituximab (1000 mg) treatment, administered intravenously on days 1 and 15. Clinical activity scores, peripheral B-lymphocyte levels, thyroid autoantibody levels, and thyroid function tests were recorded at baseline, 4 weeks, 8 weeks, 12 weeks, 24 weeks, 36 weeks, and 52 weeks after the second infusion. The primary endpoint was a change from baseline in CAS. Thyroid-stimulating immunoglobulin and thyroid-stimulating hormone levels were also monitored over the 12-month post-infusion observation period. Clinical activity scores demonstrated a statistically significant decrease from baseline at each of the follow-up visits. Thyroid-stimulating immunoglobulin and thyroid-stimulating hormone levels demonstrated no statistically significant change from baseline. B-cell depletion was observed within 1 month after rituximab treatment, and peripheral B-lymphocyte counts started to increase 36 weeks after the infusion. B-cell depletion was well-tolerated, and there were no adverse effects of the rituximab infusions. The authors concluded that CAS were significantly reduced over time in this group of 12 patients and appeared to be associated with rituximab infusion. However, the variable natural history of TED makes it difficult to definitively assign efficacy. The results support the continued investigation of rituximab for TED in a larger placebo-controlled trial.

Bartalena (2010) noted that treatment of Graves’ orbitopathy (GO) is a major challenge, and the outcome of medical therapy is unsatisfactory in about 1/3 of cases. Glucocorticoids are the first-line therapy for moderate-to-severe and active GO, more commonly given through the intravenous route. Uncertainty remains as to the best therapeutic approach when the initial glucocorticoid treatment provides an incomplete response or no response. The choice largely depends on personal experience because of the limited evidence in this field. In the author’s view, if a first course of glucocorticoids provides a suboptimal response, a second course of intravenous (or oral) glucocorticoids associated with orbital radiotherapy should be given. An alternative might be represented by oral glucocorticoids associated
with cyclosporine. The use of biological agents, the most promising being rituximab, is for the time being experimental and warrants support from randomized clinical trials.

Konno (2013) stated that evidence of rituximab’s effectiveness in myasthenia gravis is mostly limited to a few case series or open-label trials. Querol and Illa (2013) noted that controlled trials of rituximab for myasthenia gravis are needed to confirm initial results from pilot studies.

McMillan et al (2011) commented that newer steroid-sparing immunomodulatory agents, such as rituximab, have not been studied extensively in children. They show promising results from case reports and retrospective cohort studies, but there is a need for comparative studies looking at their relative efficacy, tolerability, and long-term adverse effects (including secondary malignancy) in children.

Evoli et al (2012) stated that rituximab is a promising treatment for refractory MuSK-MG; in uncontrolled studies, nearly all treated patients achieved significant improvement with substantial decrease of medication. The authors noted that it is yet to be clarified whether the early use of rituximab could prevent the permanent bulbar weakness, which constitutes a relevant disability in these patients.

Sadnicka et al (2011) reported the findings of a 76-year-old man with a pre-existing diagnosis of myasthenia gravis who was admitted to an intensive care unit with pneumonia and type II respiratory failure. In addition, muscle weakness, widespread myokymia, neuropsychiatric disturbance and autonomic disturbance were present. Anti-voltage gated potassium channel antibodies, anti-striated muscle antibodies and anti-acetylcholine receptor antibodies were positive. Nerve-conduction studies demonstrated findings consistent with patchy demyelination. Electromyography confirmed widespread myokymia, and there was evidence of diffuse encephalopathy on electroencephalography. Diagnoses of Morvan syndrome and chronic inflammatory demyelinating polyradiculopathy (CIDP) were made.

Treatment with intravenous immunoglobulin, plasma exchange and high-dose steroids were ineffective, and the patient remained dependent on mechanical ventilation. The co-existence of possibly 3 humorally mediated autoimmune diseases led to treatment with rituximab. Rituximab treatment was followed by an improvement in muscle strength, allowing successful weaning from mechanical ventilation, diminution in myokymia and improved cognition. At follow-up, there was reversal of the neuropsychiatric manifestations and normal muscle strength. This case suggested that rituximab may be useful in the treatment of autoimmune neurological disease refractory to other immunosuppressant therapies. Specifically, it added further evidence for the use of rituximab in CIDP. As indications for rituximab in humorally mediated disease continue to expand, international multi-center randomized controlled trials are needed to prove the effectiveness of this important emerging biological agent.

In a retrospective study, Nowak et al (2011) reported the results of 14 refractory generalized myasthenia gravis patients (6 AChR+; 8 MuSK+) treated with rituximab. Sustained clinical improvement was observed in all patients as well as a reduction of conventional immunotherapies. Prednisone dose decreased a mean of 65.1 %, 85.7 %, and 93.8 % after cycle 1, 2, and 3 of rituximab therapy, respectively. A statistically significant reduction in plasma exchange sessions was seen after cycle 1 with all patients being off of plasma exchange after cycle 3. Acetylcholine receptor antibody titers decreased a mean of 52.1 % (p = 0.0046) post-cycle 2. The authors concluded that these findings supported the hypothesis that rituximab is beneficial and well-tolerated in managing refractory myasthenia gravis and nearly doubles published cases. These investigators proposed that B-cell-directed therapies may become an attractive option and suggested pursuit of a prospective trial.

Díaz-Manera et al (2012) noted that rituximab has emerged as an efficacious option for drug-resistant myasthenia gravis (MG). However, reports published only describe the short-term follow-up of patients treated and little is known about their long-term clinical and immunologic evolution. These researchers reported the clinical and immunologic long-term follow-up of 17 patients (6 MuSK+MG and 11 AChR+MG) and compared the response between AChR+MG and MuSK+MG patients. Myasthenia Gravis Foundation America post-intervention status and changes in treatment and antibody titers were periodically determined. Lymphocyte subpopulations, total immunoglobulin, immunoglobulin G (IgG) anti-MuSK subclasses, and anti-tetanus toxoid IgG before and after treatment were also studied. After a mean post-treatment period of 31 months, 10 of the AChR+MG patients improved but 6 of them needed re-infusions. In contrast, all MuSK+MG patients achieved a remission (4/6) or minimal manifestations (2/6) status and no re-infusions were needed. Consequently, in the MuSK+MG group, prednisone doses were significantly reduced and concomitant immunosuppressants could be withdrawn. Clinical improvement was associated with a significant decrease in the antibody titers only in the 6 MuSK+MG patients. At last follow-up, MuSK antibodies were negative in 3 of these patients and showed a decrease
Rituximab (Rituxan) is a monoclonal antibody that targets the CD20 antigen found on the surface of B cells. It is primarily used for the treatment of various types of lymphoma and autoimmune diseases. Rituximab was initially approved for the treatment of non-Hodgkin's lymphoma (NHL) and rheumatoid arthritis (RA). Over time, its use has expanded to include other conditions, such as systemic lupus erythematosus (SLE), multiple myeloma, and chronic lymphocytic leukemia (CLL).

Rituximab works by attaching to the CD20 antigen on B cells, causing the immune system to destroy these cells. It is often administered in combination with other medications or therapies, depending on the condition being treated.

Disability was assessed using the annualized relapse rate (ARR) and response to treatment. Patients who had muscle-specific kinase (MuSK(+)) or acetylcholine receptor (AChR(+)) antibodies were included. A total of 6 patients were identified who met the criteria described. All patients tolerated rituximab without side effects and had a reduced need for immunosuppressants and/or improvement in clinical function. Patients with refractory MG appeared to respond to rituximab in this small, retrospective study. The authors concluded that these findings suggested that a larger, prospective trial is indicated.

Sadnicka et al (2011) reported the case of a 76-year old man with a pre-existing diagnosis of MG who was admitted to an intensive care unit with pneumonia and type II respiratory failure. In addition, muscle weakness, widespread myokymia, neuropsychiatric disturbance and autonomic disturbance were present. Anti-voltage gated potassium channel antibodies, anti-striated muscle antibodies and anti-acetylcholine receptor antibodies were positive. Nerve-conduction studies demonstrated findings consistent with patchy demyelination. Electromyography confirmed widespread myokymia, and there was evidence of diffuse encephalopathy on electroencephalography. Diagnoses of Morvan syndrome and chronic inflammatory demyelinating polyradiculopathy (CIDP) were made. Treatment with intravenous immunoglobulin, plasma exchange and high-dose steroids were ineffective, and the patient remained dependent on mechanical ventilation. The co-existence of possibly 3 humorally-mediated autoimmune diseases led to treatment with rituximab. Rituximab treatment was followed by an improvement in muscle strength, allowing successful weaning from mechanical ventilation, diminution in myokymia and improved cognition. At follow-up, there was reversal of the neuropsychiatric manifestations and normal muscle strength. This case suggested that rituximab may be useful in the treatment of autoimmune neurological disease refractory to other immunosuppressant therapies. Specifically, it adds further evidence for the use of rituximab in CIDP. As indications for rituximab in humorally-mediated disease continue to expand, international multi-center RCTs are needed to prove the effectiveness of this important emerging biological agent.

Ferreri and co-workers (2011) noted that systemic administration of rituximab has varying response rates with different types of lymphoma, generally with a mild toxicity level. Intralesional administration of this drug has increased local disease control in cases of cutaneous mucosa-associated lymphoid tissue (MALT) lymphoma. In a pilot study, these researchers evaluated the tolerability and activity of the intralesional administration of rituximab in patients with conjunctival B-cell lymphoma. Two patients with conjunctival MALT lymphoma refractory to previous systemic treatment with rituximab and 1 patient with relapsed follicular lymphoma of the eyelid were included in the study. Patients received 4 weekly intralesional injections followed by 6 monthly injections of undiluted rituximab together with xylocaine 2 %. Side effects and tumor response were assessed before each intralesional injection and at 3-month intervals after treatment conclusion. The 2 conjunctival MALT lymphoma patients achieved complete remission after intra-conjunctival rituximab treatment, which shows that this method of administration can overcome the primary resistance to this monoclonal antibody. The patient with the eyelid follicular lymphoma did not achieve tumor regression after the first intralesional injections of rituximab. In this patient, the addition of autologous serum resulted in lymphoma remission at the end of treatment, suggesting that drug inefficacy can be related to the low bioavailability of effectors in the tumor tissue.
Rituximab (Rituxan)

The authors concluded that although follow-up is still short, these preliminary findings suggest that intratumoral rituximab is a well-tolerated strategy in marginal-zone and follicular lymphomas of the conjunctiva. An increased bioavailability of effectors in the tumor tissue, by means of the addition of autologous serum, may improve rituximab activity. This strategy could be used in other extranodal CD20+ indolent lymphomas to improve local control, even in patients who are initially refractory to systemic rituximab treatment. They stated that response duration and potential late effects remain to be defined, and a large, prospective, clinical trial to address this promising therapeutic technique, both in ocular adnexal lymphoma and other extra-nodal lymphomas, is needed.

Salles and colleagues (2011) assessed the potential benefit of 2 years of rituximab maintenance after first-line treatment in patients with follicular lymphoma receiving a rituximab plus chemotherapy regimen. The randomized, open-label PRIMA (Primary Rituxan and Maintenance) study was undertaken in 223 centers in 25 countries. A total of 1,217 patients with previously untreated follicular lymphoma needing systemic therapy received 1 of 3 non-randomized immunochemotherapy induction regimens used in routine practice. A total of 1,019 patients achieving a complete or partial response were then randomly assigned to receive 2 years of rituximab maintenance therapy (375 mg/m² every 8 weeks) or observation. Treatment was assigned equally by randomized block randomization, stratified by induction regimen, response, region, and center. Neither the participants nor those giving the interventions, assessing outcomes, and analyzing data were masked to group assignments. The primary endpoint was progression-free survival (PFS). Analysis was by intention-to-treat. A total of 505 patients were assigned to rituximab maintenance and 513 to observation (1 patient died during randomization). With a median follow-up of 36 months (IQR 30 to 42), PFS was 74.9 % (95 % CI: 70.9 to 78.9) in the rituximab maintenance group (130 patients progressed) and 57.6 % (53.2 to 62.0) in the observation group (218 progressed; hazard ratio [HR] 0.55, 95 % CI: 0.44 to 0.68, p < 0·0001). Two years after randomization, 361 patients (71.5 %) in the rituximab maintenance group were in complete or unconfirmed complete response versus 268 (52.2 %) in the observation group (p = 0·0001). Overall survival did not differ significantly between groups (HR 0·87, 95 % CI: 0·51 to 1·47). Grade 3 and 4 adverse events were recorded in 121 patients (24 %) in the rituximab maintenance group and 84 (17 %) in the observation group (risk ratio 1·46, 95 % CI: 1·14 to 1·87; p = 0·0026). Infections (grades 2 to 4) were the most common adverse event, occurring in 197 (39 %) and 123 (24 %) patients, respectively (risk ratio 1·62, 95 % CI: 1·35 to 1·96; p < 0·0001). The authors concluded that 2 years of rituximab maintenance therapy after immunochemotherapy as first-line treatment for follicular lymphoma significantly improves PFS.

In January 2011, the FDA approved the use of rituximab as maintenance therapy for advanced follicular lymphoma in patients with an initial response to induction therapy with the drug plus chemotherapy. The approval was based on results of the afore-mentioned PRIMA study, which showed that showing continuing rituximab administration every 2 months for 2 years in patients who responded to initial treatment with rituximab plus chemotherapy, nearly doubled the likelihood of them living without the disease worsening (PFS) compared to those who stopped treatment (based on a HR of 0.54, 95 % CI: 0.42 to 0.70; p < 0·0001).

Neuromyelitis optica (NMO, Devic's syndrome), long considered a clinical variant of multiple sclerosis, is now regarded as a distinct disease entity (Trebst, et al., 2014). Major progress has been made in the diagnosis and treatment of NMO since aquaporin-4 antibodies (AQP4-Ab; also termed NMO-IgG) were first described in 2004. The Neuromyelitis Optica Study Group (NEMOS) stated that NMO Testing of AQP4-Ab is essential and is the most important test in the diagnostic work-up of suspected NMO, and helps to distinguish NMO from other autoimmune diseases. In addition, imaging techniques, particularly magnetic resonance imaging of the brain and spinal cord, are obligatory in the diagnostic workup. The NEMOS stated that it is important to note that brain lesions in NMO and NMOSD are not uncommon, do not rule out the diagnosis, and show characteristic patterns. Other imaging modalities such as optical coherence tomography are proposed as useful tools in the assessment of retinal damage. Therapy of NMO should be initiated early. The NEMOS suggested azathioprine and rituximab as first-line treatments, the latter being increasingly regarded as an established therapy with long-term efficacy and an acceptable safety profile in NMO patients. Other immunosuppressive drugs, such as methotrexate, mycophenolate mofetil and mitoxantrone, are recommended as second-line treatments. Promising new therapies are emerging in the form of anti-IL6 receptor, anti-complement or anti-AQP4-Ab biologicals.

In an open label study, Cree et al (2005) reported their findings of 8 patients with worsening neuromyelitis optica who were treated with rituximab. Treatment was well-tolerated; 6 of 8 patients were relapse free and median attack rate declined from 2.6 attacks/patient/year to 0 attacks/patient/year (p = 0.0078). Seven of 8 patients experienced substantial recovery of neurological function over 1 year of
average follow-up. The pre-treatment median Expanded Disability Status Scale score was 7.5, and at follow-up examination was 5.5 (p = 0.013). These investigators noted that the apparently robust effects of rituximab deserve further investigation through controlled trials.

In a prospective, open-label study, Kim and colleagues (2011) evaluated the safety and effectiveness of repeated rituximab treatment based on the assessment of peripheral circulating memory B cells over 24 months in patients with relapsing neuromyelitis optica (NMO). A total of 30 patients with relapsing NMO or NMO spectrum disorder were included in this study. Treatment protocol of rituximab consisted of an induction therapy (375 mg/m² once-weekly for 4 weeks or 1,000 mg infused twice, with a 2-week interval between the infusions) followed by maintenance therapy. The maintenance therapy was repeated treatment with rituximab (375 mg/m², once) whenever the frequency of reemerging CD27+ memory B cells was more than 0.05 % in peripheral blood mononuclear cells by flow cytometric analysis. Main outcome measures included annualized relapse rate, disability (Expanded Disability Status Scale score), anti-aquaporin 4 antibody level, and safety of rituximab treatment. Of 30 patients, 28 showed a marked reduction in relapse rate while taking rituximab over 24 months. The relapse rate was reduced significantly, by 88 %, and 70 % of patients became relapse-free over 24 months. Disability either improved or stabilized in 97 % of patients. Anti-aquaporin 4 antibody levels declined significantly following treatment with rituximab, consistent with the clinical response and the effect on CD27+ memory B cells. Repeated treatment with rituximab was generally well-tolerated, and no clinically relevant adverse event leading to discontinuation of treatment was observed. The authors concluded that repeated treatment with rituximab appeared to produce consistent and sustained efficacy over 24 months with good tolerability in patients with NMO.

Pellkofer et al (2011) performed a prospective long-term cohort study of 10 patients with NMO who were treated up to 5 times with rituximab as a second-line therapy. Clinical examinations, B-cell counts, and serum concentrations of BAFF (B-cell activating factor of the TNF family; also called TNFSF13b), APRIL (a proliferation-inducing ligand; also called TNFSF13b), AQP4-ab, and immunoglobulin levels were measured every 3 months. Repeated treatment with rituximab led to sustained clinical stabilization in most patients with NMO. Disease activity correlated with B-cell depletion, but not clearly with AQP4-ab or levels of APRIL. BAFF levels increased after application of rituximab and indicated persisting efficacy of the drug but did not correlate with disease activity. Overall, rituximab was well-tolerated even after up to 5 consecutive treatment courses; however, several severe adverse reactions were observed. The authors concluded that these data indicated that long-term therapy with rituximab is effective in NMO as a second-line therapy and has an acceptable safety profile. Re-treatment with rituximab should be applied before re-appearance of circulating B cells.

The American Academy of Neurology's guideline on "Clinical evaluation and treatment of transverse myelitis" (Scott et al, 2011) assessed the evidence for diagnostic tests and therapies for transverse myelitis (TM) and made evidence-based recommendations. A review of the published literature from 1966 to March 2009 was performed, with evidence-based classification of relevant articles. Level B recommendations: NMO-immunoglobulin G (IgG) antibodies should be considered useful to determine TM cause in patients presenting with clinical acute complete transverse myelitis (ACTM) features. The presence of NMO-IgG antibodies (aquaporin-4-specific antibodies) should be considered useful in determining increased TM recurrence risk. Level C recommendations: in suspected TM, distinction between ACTM or acute partial transverse myelitis may be considered useful to determine TM etiology and risk for relapse (more common with APTM). Age and gender may be considered useful to determine etiology in patients presenting with TM syndrome, with spinal infarcts seen more often in older patients and more female than male patients having TM due to multiple sclerosis (MS). Brain MRI characteristics consistent with those of MS may be considered useful to predict conversion to MS after a first partial TM episode. Longer spinal lesions extending over greater than 3 vertebral segments may be considered useful in determining NMO versus MS. CSF examination for cells and oligoclonal bands may be considered useful to determine the cause of the TM syndrome. Plasma exchange may be considered in patients with TM who fail to improve after corticosteroid treatment. Rituximab may be considered in patients with TM due to NMO to decrease the number of relapses. Level U recommendations: there is insufficient evidence to support or refute the efficacy of other TM therapies or the usefulness of ethnicity to determine the cause of a subacute myelopathy.

Arampatzis et al (2011) presented a rare case of chronic lymphocytic leukemia (CLL)-associated focal segmental glomerulosclerosis (FSGS) with nephrotic-range proteinuria. A 53-year old Caucasian man, previously healthy, with no history of hypertension, alcohol use or smoking presented with rapid weight gain, massive peripheral edema, and hypertension. Laboratory findings included a white blood cell count...
of 49,800 cells/mm³ with an absolute lymphocyte count of 47,000 cells/mm³, serum albumin of 2.3 g/dL, urea 65 mg/dL, and creatinine 1.5 mg/dL. A 24-hour urine collection contained 7.1 g protein and significant hematuria. A peripheral blood smear showed mature lymphocytosis and smearage cells. Diagnostic imaging showed mild para-aortic lymphadenopathy with no renal abnormalities. Bone marrow aspiration and trephine biopsy showed diffuse and focal infiltration with B-CLL lymphocytes. Percutaneous renal biopsy revealed total sclerosis in 3/21 (14%) of the glomeruli and focal and segmental solidification and sclerosis in 4/21 (19%) glomeruli. A regimen of fludarabine, cyclophosphamide and rituximab was successful in inducing remission of the CLL and clinical resolution of the nephritic-range proteinuria. The authors concluded that a multi-disciplinary approach to monitor both the malignancy and the glomerular lesions is crucial for the optimal management of paraneoplastic glomerulonephritis. They noted that although chemotherapy with fludarabine, cyclophosphamide and rituximab successfully treated CLL-associated nephrotic syndrome in this patient, further studies are required to confirm efficacy in this setting.

In a systematic review, Araya and Dharnidharka (2011) stated that recurrence of FSGS occurs in 30 to 40% of allografts. Therapies for recurrence are not well established. These researchers retrieved all published reports depicting kidney transplant recipients with FSGS recurrence, treated with rituximab, to determine factors associated with treatment response. They found 18 reports of 39 transplant recipients who received rituximab. By uni-variate analysis for 2 outcomes (no response versus any response), fewer rituximab infusions and normal serum albumin at recurrence were associated with treatment response. For 3 outcomes (no response, partial and complete remission), male gender, fewer rituximab infusions, shorter time to rituximab treatment, and normal serum albumin were associated with remission. Multi-variate analysis for both models revealed that normal serum albumin at FSGS recurrence and lower age at transplant were associated with response. The authors noted that rituximab for recurrence of FSGS may be beneficial for only some patients. A younger age at transplant and normal serum albumin level at recurrence diagnosis may predict response.

Also, an UpToDate review on “Treatment of primary focal segmental glomerulosclerosis” (Appel and Cattran, 2012) does not mention the use of rituximab.

Tracy and Dyck (2010) examined the data for treatment of inflammatory demyelinating peripheral neuropathies, particularly chronic inflammatory demyelinating polyneuropathy (CIDP). A large clinical trial showed short and long-term efficacy of IVIG for the treatment of CIDP and the U.S. Food and Drug Administration approved the use of IVIG (Gamunex) as a treatment for CIDP. Recent trials for other agents for CIDP treatment have not proved as promising, with a large study of methotrexate failing to show significant benefit. There are recent cases of monoclonal antibodies (e.g., rituximab, alemtuzumab) showing benefit in patients with CIDP, but the side effect profiles can be worrisome.

Nobile-Orazio et al (2010) stated that CIDP and MMN usually respond to immune therapies including steroids and plasma exchange for CIDP and high-dose IVIGs for both diseases. Other immune therapies have been used to reduce the costs or the side-effects of these therapies, but their efficacy was only recently assessed in randomized controlled trials (RCTs). The prolonged efficacy of IVIG in CIDP has been confirmed in a 48-week RCT. Two other RCTs showed that oral methotrexate or intramuscular interferon beta were not more effective than placebo in improving the efficacy or reducing the dose of IVIG or steroids. In MMN, a RCT showed that oral mycophenolate mofetil was not more effective than placebo in increasing the efficacy or reducing the dose of IVIG. Other immune therapies were assessed in open trials in both diseases, but their efficacy remains unclear, even if in some patients a possible efficacy of rituximab was reported. Some preliminary studies suggest that subcutaneous immunoglobulin may be as effective as IVIG in the maintenance therapy of CIDP and MMN. The authors concluded that after several years of anecdotal reports, a number of RCT have now appeared in CIDP and MMN, but their results are still insufficient to support the use of new therapies in these diseases.
In a retrospective, observational and multi-center study, Benedetti et al (2011) analyzed the efficacy of rituximab in a large CIDP cohort. A total of 13 CIDP patients were treated with rituximab after the partial or complete lack of efficacy of conventional therapies. Eight patients had co-occurring hematological diseases. Patients who improved by at least 2 points in standard clinical scales, or who reduced or discontinued the pre-rituximab therapies, were considered as responders. Nine patients (7 with hematological diseases) responded to rituximab: 6 of them, who were non-responders to conventional therapies, improved clinically, and the other 3 maintained the improvement that they usually achieved with IVIG or plasma exchange. Significantly associated with shorter disease duration, rituximab responses started after a median period of 2.0 months (range of 1 to 6) and lasted for a median period of 1 year (range of 1 to 5). The authors concluded that rituximab seems to be a promising therapeutic choice when it targets both CIDP and co-occurring hematological diseases.

In a Cochrane review, Mahdi-Rogers (2010) systematically reviewed the evidence from RCTs of cytotoxic drugs and interferons other than corticosteroids, immunoglobulin and plasma exchange for CIDP. These researchers sought RCTs and quasi-randomized trials of all immunosuppressive agents such as azathioprine, cyclophosphamide, methotrexate, ciclosporin A, mycophenolate mofetil, and rituximab and all immunomodulatory agents such as interferon alfa and interferon beta in participants fulfilling standard diagnostic criteria for CIDP. Two authors independently selected trials, judged their methodological quality and extracted data. They wanted to measure the change in disability after 1 year as the primary outcome. Secondary outcomes were change in disability after 4 or more weeks (from randomization), change in impairment after at least 1 year, change in maximum motor nerve conduction velocity and compound muscle action potential amplitude after 1 year and for those participants who were receiving corticosteroids or IVIG, the amount of this medication given during at least 1 year after randomization. Participants with one or more serious adverse events during the first year was also a secondary outcome. Four trials fulfilled the selection criteria, one of azathioprine (27 participants), 2 of interferon beta-1a (77 participants in total) and 1 of methotrexate (60 participants). None of these trials showed significant benefit in the primary outcome or secondary outcomes selected for this review. The evidence from RCTs does not show significant benefit from azathioprine, interferon beta-1a or methotrexate but none of the trials was large enough to rule out small or moderate benefit. The evidence from observational studies is insufficient to avoid the need for RCTs to discover whether these drugs are beneficial. Future trials should have improved designs, more sensitive outcome measures and longer durations.

In a multi-center prospective study, Bader-Meunier and associates (2011) evaluated the safety and effectiveness of rituximab in juvenile dermatomyositis (JDM) in off-trial patients. A total of 9 patients with severe JDM were studied. The main indication for rituximab treatment was severe and/or refractory muscle involvement (7 patients), severe calcinosis (1 patient), or severe chronic abdominal pain associated with abdominal lipomatosis (1 patient). Rituximab was associated with corticosteroids, immunosuppressive drugs, and plasma exchange therapy in 9/9, 5/9, and 2/9 patients, respectively. Mild infections of the calcinosis sites occurred in 2 patients and an infusion-related event in 1. Complete clinical response was achieved in 3/6 patients treated with rituximab for muscle involvement. In these responders steroid therapy was stopped or tapered to less than 15 % of the baseline dosage, with no relapse, with a follow-up ranging from 1.3 to 3 years. Calcinosis did not improve in the 6 affected patients. The authors concluded that this small series suggested that rituximab may be effective for treating muscle and skin involvement in a small subset of children with severe JDM, and that its safety profile was satisfactory. Moreover, they stated that further studies are needed to identify predictive factors of response to rituximab in patients with severe JDM.

Arce-Salinas et al (2012) reported the findings of 8 patients with refractory lupus nephritis (LN) who received rituximab after failing standard sequential therapy and were followed for 104 weeks after the infusion. One patient died secondary to a complicated pregnancy but had stable renal function; 3 patients received a re-infusion of rituximab approximately 12 months apart due to a renal flare; and during the 2nd year of follow-up, those patients progressed toward end-stage renal disease. The 4 remaining patients demonstrated improvements in Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score, creatinine clearance, and proteinuria with maintenance of their standard immunosuppressive therapy and did not require a re-infusion of rituximab. The authors concluded that although rituximab as induction therapy for refractory LN has been shown to have a good response, its effectiveness in long-term assessments demonstrated disappointing results.
In a randomized, double-blind, placebo-controlled phase 3 trial (LUNAR study), Rovin et al (2012) evaluated the safety and effectiveness of rituximab in LN patients treated concomitantly with mycophenolate mofetil (MMF) and corticosteroids. Patients (n = 144) with Class III or IV LN were randomized 1:1 to rituximab (1,000 mg) or placebo on days 1, 15, 168, and 182. The primary endpoint was renal response status at week 52. Rituximab depleted peripheral CD19+ B cells in 71/72 patients. Complete and partial renal responses were achieved in 33/72 (45.8 %) placebo- and 41/72 (56.9 %) rituximab-treated patients (p = 0.55), the difference mostly accounted for by partial responses. The primary endpoint (superior response rate with rituximab) was not achieved. Eight placebo patients and no rituximab-treated patients required cyclophosphamide rescue therapy through week 52. Statistically significant improvements in serum complement C3, C4, and anti-dsDNA antibody levels were observed with rituximab. In both treatment groups, a reduction in anti-dsDNA greater than the median reduction was associated with improvement in proteinuria. Rates of serious adverse events, including infections, were similar in both groups. Neutropenia, leukopenia, and hypotension occurred more frequently in the rituximab group. The authors concluded that although rituximab therapy led to more responders and greater reductions in anti-dsDNA and C3/C4 levels, it did not improve clinical outcomes after 1 year of treatment. The combination of rituximab with MMF and corticosteroids did not result in any new or unexpected safety signals.

Also, an UpToDate review on "Therapy of diffuse or focal proliferative lupus nephritis" (Falk et al, 2012) does not mention the use of rituximab as a therapeutic option.

The National Institutes of Health (NIH) Office of Rare Diseases Research states that Rosai-Dorfman disease is a benign disease which is characterized by over-production and accumulation of a specific type of white blood cell (histiocyte) in the lymph nodes of the body, most often those of the neck. Other lymph node groups may also be involved and, in some cases, abnormal accumulation of histiocytes may occur in other areas of the body. The cause of this condition, which was first described by Rosai and Dorfman in 1969, remains unknown. It has been hypothesized that altered immune responses and infectious agents may play a role. Sinus histiocytosis with massive lymphadenopathy disease (SHML) is a self-limited and seldom life-threatening disease which commonly does not require therapy.

The NIH Office of Rare Diseases Research further reports that in many cases the signs and symptoms of Rosai-Dorfman disease resolve without any treatment (spontaneous remission) and that this generally occurs within months to a few years. The preferred course of management is continuous observation without treatment when possible. Many individuals will not require therapy, but in some cases, various treatment options may become necessary and are typically directed toward the affected individual’s specific symptoms. Some individuals may need surgical removal of histiocyte lesions.[4] In more serious cases, treatment options have included therapy with certain drugs including steroids (e.g., prednisone), alfa-interferon (a man-made copy of a protein that is normally made by the body in response to infection), chemotherapy and radiation therapy. However, these treatments have improved symptoms in some individuals, but in others they have not been effective.

McClain et al (2004) stated that SHML most often presents as painless cervical lymphadenopathy, although many patients can have extranodal involvement as well and that case series reports vary greatly with regard to treatment of SHML. Many patients have spontaneous regression or resolution following surgical removal of isolated node groups. McClain et al (2004) further stated that “others with systemic involvement may benefit from chemotherapy, but no clinical trials have been done.” There are no clinical trials currently published in the peer-reviewed literature examining a role of rituximab in treatment of Rosai-Dorfman disease.

Wink et al (2011) noted that cryoglobulinemia associated with systemic vasculitis mediated by immune complexes is a rare combination. These immune complexes are composed of immunoglobulins and precipitate when exposed to cold temperature. Cryoglobulinemic vasculitis, treated or untreated, may lead to substantial morbidity and even mortality. Novel targeted therapies may well provide new therapeutic options following or perhaps even prior to the classical cytotoxic therapies. Systemic B cell depletion with rituximab, a chimeric monoclonal antibody against CD20 antigen, is commonly applied in patients with non-Hodgkin’s lymphoma or in refractory rheumatoid factor-positive rheumatoid arthritis. Since B cell clones are the source of cryoglobulins, therapeutic effectiveness of rituximab in cryoglobulinemic vasculitis may be expected. These researchers described a 72-year old woman with mixed cryoglobulinemia type 2, who has successfully been treated with rituximab infusions after failing on prednisone and azathioprine. They reviewed the literature and found 142 cases of cryoglobulinemic
vasculitis, 138 mixed (type 2 or 3) and 4, type 1. Rituximab was applied mostly after failure on other treatments. Significant reduction in levels of rheumatoid factor, cryoglobulins and IgM were reported after rituximab therapy. Of the total 142, cases 119 could be evaluated for the response on rituximab therapy, the other 23 cases only regarding side effects. Of the 119 evaluated patients, 71 (60 %) had complete response; 28 (23 %), partial response and 20 patients (17 %), no response. Data were not blinded or placebo-controlled. Side effects were seen in 27 of the 142 patients. Occurrence of the side effects was associated with high baseline levels of cryoglobulins, with a high-dose of rituximab infusion of 1,000 mg and with a high level of complement activation. Death was reported four times and was related with the disease.

Pietrogrande et al (2011) defined a core set of recommendations for the treatment of HCV-associated mixed cryoglobulinemia syndrome (MCS) by combining current evidence from clinical trials and expert opinion. Expert physicians involved in studying and treating patients with MCS formulated statements after discussing the published data. Their attitudes to treatment approaches (particularly those insufficiently supported by published data) were collected before the consensus conference by means of a questionnaire, and were considered when formulating the statements. An attempt at viral eradication using pegylated interferon plus ribavirin should be considered the first-line therapeutic option in patients with mild-moderate HCV-related MCS. Prolonged treatment (up to 72 weeks) may be considered in the case of virological non-responders showing clinical and laboratory improvements. Rituximab (RTX) should be considered in patients with severe vasculitis and/or skin ulcers, peripheral neuropathy or glomerulonephritis. High-dose pulsed glucocorticoid (GC) therapy is useful in severe conditions and, when necessary, can be considered in combination with RTX; on the contrary, the majority of conference participants discouraged the chronic use of low-medium GC doses. Apheresis remains the elective treatment for severe, life-threatening hyper-viscosity syndrome; its use should be limited to patients who do not respond to (or who are ineligible for) other treatments, and emergency situations. Cyclophosphamide can be considered in combination with apheresis, but the data supporting its use are scarce. Despite the limited available data, colchicine is used by many of the conference participants, particularly in patients with mild-moderate MCS refractory to other therapies. Careful monitoring of the side effects of each drug, and its effects on HCV replication and liver function tests is essential. A low-antigen-content diet can be considered as supportive treatment in all symptomatic MCS patients.

Although there are no data from controlled trials, controlling pain should always be attempted by tailoring the treatment to individual patients on the basis of the guidelines used in other vasculitides. The authors concluded that although there are few controlled randomized trials of MCS treatment, increasing knowledge of its pathogenesis is opening up new frontiers. The recommendations provided may be useful as provisional guidelines for the management of MCS.

De Vita et al (2012) conducted a long-term, prospective, randomized controlled trial evaluating RTX therapy for severe mixed cryoglobulinemia (MC) or cryoglobulinemic vasculitis (CV). A total of 59 patients with CV and related skin ulcers, active glomerulonephritis, or refractory peripheral neuropathy were enrolled. In CV patients who also had HCV infection, treatment of the HCV infection with anti-viral agents had previously failed or was not indicated. Patients were randomized to the non-RTX group (to receive conventional treatment, consisting of 1 of the following 3: glucocorticoids; azathioprine or cyclophosphamide; or plasmapheresis) or the RTX group (to receive 2 infusions of 1 g each, with a lowering of the glucocorticoid dosage when possible, and with a second course of RTX at relapse). Patients in the non-RTX group who did not respond to treatment could be switched to the RTX group. Study duration was 24 months. Survival of treatment at 12 months (i.e., the proportion of patients who continued taking their initial therapy), the primary end point, was statistically higher in the RTX group (64.3 % versus 3.5 % [p < 0.0001]), as well as at 3 months (92.9 % versus 13.8 % [p < 0.0001]), 6 months (71.4 % versus 3.5 % [p < 0.0001]), and 24 months (60.7 % versus 3.5 % [p < 0.0001]). The Birmingham Vasculitis Activity Score decreased only after treatment with RTX (from a mean +/- SD of 11.9 +/- 5.4 at baseline to 7.1 +/- 5.7 at month 2; p < 0.001) up to month 24 (4.4 +/- 4.6; p < 0.0001). Rituximab appeared to be superior therapy for all 3 target organ manifestations, and it was as effective as conventional therapy. The median duration of response to RTX was 18 months. Overall, RTX treatment was well-tolerated. The authors concluded that rituximab monotherapy represents a very good option for severe CV and can be maintained over the long-term in most patients.

Sneller et al (2012) conducted a single-center, open-label, randomized controlled trial of rituximab (375 mg/m(2)/week for 4 weeks) compared to the best available therapy (maintenance or increase in immunosuppressive therapy) for HCV-associated CV in patients in whom anti-viral therapy had failed to induce remission. The primary end point was disease remission at 6 months from study entry. A total of 24 patients were enrolled (12 in each treatment group). Baseline disease activity and organ involvement
were similar in the two groups. Ten patients in the rituximab group (83%) were in remission at study month 6, as compared with 1 patient in the control group (8%), a result that met the criterion for stopping the study (p < 0.001). The median duration of remission for rituximab-treated patients who reached the primary end point was 7 months. No adverse effects of rituximab on HCV plasma viremia or on hepatic transaminase levels were observed. The authors concluded that rituximab was a well-tolerated and effective treatment in patients with HCV-associated CV in whom anti-viral therapy failed to induce remission.

Primary Sjögren's syndrome (pSS) is an autoimmune disorder affecting exocrine glands; however, a subgroup of pSS patients experience systemic extra-glandular involvement leading to a worsening of disease prognosis (Carubbi, et al., 2013). Current therapeutic options are mainly empiric and often translated by other autoimmune diseases. In the last few years growing evidence suggests that B-cell depletion by rituximab (RTX) is effective also in pSS. Patients with early active disease appear to be those who could benefit the most from RTX.

A systematic evidence review concluded that further clinical trials are necessary to establish the efficacy of rituximab in primary Sjögren syndrome. Ramos-Casals, et al (2010) searched MEDLINE and EMBASE for articles on drug therapy for primary Sjögren syndrome published between January 1, 1986, and April 30, 2010. Controlled trials of topical and systemic drugs including adult patients with primary Sjögren syndrome were selected as the primary information source. The search strategy yielded 37 trials. The authors reported that a placebo-controlled trial found significant improvement in the Schirmer and corneal staining scores, blurred vision, and artificial tear use in patients treated with topical ocular 0.05% cyclosporine. Three placebo-controlled trials found that pilocarpine was associated with improvements in dry mouth (61%-70% vs 24%-31% in the placebo group) and dry eye (42%-53% vs 26%). Two placebo-controlled trials found that cevimeline was associated with improvement in dry mouth (66%-76% vs 35%-37% in the placebo group) and dry eye (39%-72% vs 24%-30%). Small trials (<20 patients) found no significant improvement in sicca outcomes for oral prednisone or hydroxychloroquine and limited benefits for immunosuppressive agents (azathioprine and cyclosporine). A large trial found limited benefits for oral interferon alfa-2a. Two placebo-controlled trials of infliximab and etanercept did not achieve the primary outcome (a composite visual analog scale measuring joint pain, fatigue, and dryness); neither did 2 small trials (<30 patients) testing rituximab, although significant results were observed in some secondary outcomes and improvement compared with baseline. The authors concluded that, in primary Sjögren syndrome, evidence from controlled trials suggests benefits for pilocarpine and cevimeline for sicca features and topical cyclosporine for moderate or severe dry eye. Anti-tumor necrosis factor agents have not shown clinical efficacy, and larger controlled trials are needed to establish the efficacy of rituximab. An accompanying editorial by Vissink, et al. (2010) stated that "larger trials are needed before the role of rituximab in the treatment of primary Sjögren syndrome can be settled, not only with respect to its effect on salivary flow rate and xerostomia but also with regard to the effect of rituximab treatment on general symptoms, extraglandular involvement, and life-threatening situations in primary Sjögren syndrome."

Carubbi, et al. (2013) conducted a study to investigate the efficacy and safety of RTX in comparison to disease modifying anti-rheumatic drugs (DMARDs) in early active pSS patients. Forty-one patients with early pSS and active disease (EULAR Sjögren's syndrome disease activity index, ESSDAI ≥ 6) were enrolled in the study. Patients were treated with either RTX or DMARDs in two different rheumatology centers and followed up for 120 weeks. Clinical assessment was performed by ESSDAI every 12 weeks up to week 120 and by self-reported global disease activity pain, sicca symptoms and fatigue on visual analogic scales, unstimulated saliva flow and Schirmer's I test at week 12, 24, 48, 72, 96, and 120. Laboratory assessment was performed every 12 weeks to week 120. Two labial minor salivary gland (MSG) biopsies were obtained from all patients at the time of inclusion in the study and at week 120. The investigators concluded that their study demonstrated that RTX treatment results in a faster and more pronounced decrease of ESSDAI and other clinical parameters compared to DMARDs treatment. No adverse events were reported in the two groups. The investigators also observed that RTX is able to reduce glandular infiltrate, interfere with B/T compartmentalization and consequently with the formation of ectopic lymphoid structures and germinal center-like structures in pSS-MSGs. The investigators reported that this is the first study performed in a large cohort of early active pSS patients for a period of 120 weeks. The investigators stated that the study showed that RTX is a safe and effective agent to be employed in pSS patients with systemic, extra-glandular involvement. Furthermore, they noted that their data on pSS-MSGs provide additional biological basis to employ RTX in this disease.
In a double-blind, randomized, placebo-controlled trial, Meijer et al (2010) examined the safety and effectiveness of rituximab in patients with primary Sjogren's syndrome (pSS). Patients with active pSS, as determined by the revised American-European Consensus Group criteria, and a rate of stimulated whole saliva secretion of greater than or equal to 0.15 ml/min were treated with either rituximab (1,000 mg) or placebo infusions on days 1 and 15. Patients were assigned randomly to a treatment group in a ratio of 2:1 (rituximab:placebo). Follow-up was conducted at 5, 12, 24, 36, and 48 weeks. The primary end point was the stimulated whole saliva flow rate, while secondary end points included functional, laboratory, and subjective variables. A total of 30 patients with pSS (29 females) were randomly allocated to a treatment group. The mean +/- SD age of the patients receiving rituximab was 43 +/- 11 years and the disease duration was 63 +/- 50 months, while patients in the placebo group were age 43 +/- 17 years and had a disease duration of 67 +/- 63 months. In the rituximab group, significant improvements, in terms of the mean change from baseline compared with that in the placebo group, were found for the primary end point of the stimulated whole saliva flow rate (p = 0.038 versus placebo) and also for various laboratory parameters (B cell and rheumatoid factor [RF] levels), subjective parameters (Multidimensional Fatigue Inventory [MFI] scores and visual analog scale [VAS] scores for sicca symptoms), and extra-glandular manifestations. Moreover, in comparison with baseline values, rituximab treatment significantly improved the stimulated whole saliva flow rate (p = 0.004) and several other variables (e.g., B cell and RF levels, unstimulated whole saliva flow rate, lacrimal gland function on the lissamine green test, MFI scores, Short-Form 36 health survey scores, and VAS scores for sicca symptoms). One patient in the rituximab group developed mild serum sickness-like disease. The authors concluded that these results indicated that rituximab is an effective and safe treatment strategy for patients with pSS.

Mekinian et al (2012) evaluated RTX in pSS with peripheral nervous system (PNS) involvement. Patients with pSS and PNS involvement who were included in the French AIR registry were analyzed. A total of 17 patients (aged 60 years (44 to 78 years); 14 were female) were included in this analysis. Neurological improvement was noted in 11 patients (65 %) at 3 months. Rankin scale decreased from 3 (1 to 5) to 2 (1 to 5), 2 (1 to 5) and 2 (1 to 6) after 3, 6 and 9 months (p = 0.02). European Sjogren's Syndrome Disease Activity Index (ESSDAI) decreased from 18 (10 to 44) to 11 (5 to 20), 11 (5 to 29) and 12 (5 to 30) after 3, 6 and 9 months (p < 0.05). Rituximab was effective in neurological involvement in 9/10 patients with vasculitis or cryoglobulinemia (90 %) (group 1) at 3 months and in 2/7 cases (29 %) without cryoglobulinemia and vasculitis (p = 0.03). Rankin and European Sjogren's Syndrome Activity Index scales decreased significantly in group 1. The authors concluded that RTX seems effective in cryoglobulinemia or vasculitis-related PNS involvement in pSS.

Gottenberg et al (2013) evaluated the safety and effectiveness of rituximab in patients with pSS. The AutoImmune and Rituximab registry has included 86 patients with pSS treated with rituximab, prospectively followed-up every 6 months for 5 years. A total of 78 patients with pSS (11 men, 67 women), who already had at least 1 follow-up visit, were analyzed. Median age was 59.8 years (29 to 83), median duration of disease was 11.9 years (3 to 32). Indications for treatment were systemic involvement for 74 patients and only severe glandular involvement in 4 patients. The median ESSDAI was 11 (2 to 31); 17 patients were concomitantly treated with another immunosuppressant agent. Median follow-up was 34.9 months (6 to 81.4) (226 patient-years). Overall efficacy according to the treating physician was observed in 47 patients (60 %) after the first cycle of rituximab. Median ESSDAI decreased from 11 (2 to 31) to 7.5 (0 to 26) (p < 0.0001). Median dosage of corticosteroid decreased from 17.6 mg/day (3 to 60) to 10.8 mg/day (p = 0.1). A total of 41 patients were retreated with rituximab; 4 infusion reactions and 1 delayed serum sickness-like disease resulted in rituximab discontinuation. Three serious infections (1.3/100 patient-years) and 2 cancer-related deaths occurred. The authors concluded that in common practice, the use of rituximab in pSS is mostly restricted to patients with systemic involvement. This prospective study showed good efficacy and tolerance of rituximab in patients with pSS and systemic involvement.

The British Society for Haematology's guidelines on thrombotic thrombocytopenic purpura (TTP) (Scully et al, 2012) recommend use of rituximab in patients with refractory or relapsing immune-mediated TTP. The guidelines also stated that rituximab should be considered on admission, in conjunction with steroids and plasmapheresis, in acute idiopathic TTP with neurological/cardiac pathology, which are associated with a high mortality. An UpToDate review on “Treatment of thrombotic thrombocytopenic purpura-hemolytic uremic syndrome in adults” (Kaplan and George, 2013) recommended the use of rituximab or cyclosporine in patients with a severe course of refractory or recurrent TTP-HUS who do not rapidly
respond to plasma exchange, worsen with neurologic abnormalities despite plasma exchange plus corticosteroids, or have relapsing disease.

An UpToDate review on “Treatment of the antiphospholipid syndrome” (Bermas et al, 2013) states that “Investigational therapies for the APS include autologous stem cell transplantation and rituximab. To date, insufficient data on the use of these approaches exist to guide therapeutic recommendations”. Furthermore, the British Committee for Standards in Haematology's guidelines on “The investigation and management of antiphospholipid syndrome” (Keeling et al, 2012) does not mention rituximab as a therapeutic option.

Khattri et al (2012) reviewed the literature on B cell directed therapies in human and experimental antiphospholipid syndrome (APS). The clinical data are limited to B cell depletion with rituximab and comprises case reports and case series. Murine studies included use of modulators of B cell function such as belimumab and abatacept. In both human and murine studies, B cell directed therapies appeared to have clinical and serologic beneficial effects including a decrease in the antiphospholipid antibody titers after treatment. The authors stated that randomized controlled clinical trials are needed to determine whether B cell depletors and/or B cell modulators can be effective agents for treating patients with APS.

In a pilot, phase II study, Erkan et al (2013) evaluated the safety of rituximab in antiphospholipid antibody (aPL)-positive patients with non-criteria manifestations of APS. The secondary objectives were to evaluate the effect of rituximab on the aPL profile and to evaluate the efficacy of rituximab treatment for non-criteria manifestations of APS. In this 12-month study, adult aPL-positive patients with thrombocytopenia, cardiac valve disease, skin ulcer, aPL nephropathy, and/or cognitive dysfunction received 2 doses of rituximab (1,000 mg) on days 1 and 15. Antiphospholipid antibody profiles and clinical outcome measures, which were categorized as complete response, partial response, no response, or recurrence, were analyzed at preset time points. Two of 19 patients experienced infusion reactions, resulting in early termination; 12 serious adverse events and 49 non-serious adverse events were recorded. All patients who had positive results of lupus anticoagulant, anti-cardiolipin, and anti-β(2) -glycoprotein I antibody tests at baseline had positive results at 24 weeks and 52 weeks. The numbers of patients with a complete response, a partial response, no response, and recurrence for the clinical outcome measures at 24 weeks were as follows: for thrombocytopenia, 1, 1, 2, and 0, respectively; for cardiac valve disease, 0, 0, 3, and not analyzed, respectively; for skin ulcer, 3, 1, 0, and 1, respectively; for aPL nephropathy, 0, 1, 0, and 0, respectively; and for cognitive dysfunction, 3, 1, 1, and not analyzed, respectively. The authors concluded that the findings of this uncontrolled and non-randomized pilot study suggested that the safety of rituximab in aPL-positive patients is consistent with the safety profile of rituximab. Despite causing no substantial change in aPL profiles, rituximab may be effective in controlling some but not all non-criteria manifestations of APS.

Uhlving et al (2012) stated that bronchiolitis obliterans (BO) following allogeneic hematopoietic SCT (HSCT) is a serious complication affecting 1.7 to 26.0 % of the patients, with a reported mortality rate of 21 to 100 %. It is considered a manifestation of chronic graft-versus-host disease (GVHD), but the knowledge of etiology and pathogenesis is still limited. The authors noted that no convincing effect of rituximab on bronchiolitis obliterans has been established.

Kemper et al (2012) noted that in patients with refractory steroid-sensitive nephrotic syndrome (SSNS), treatment with rituximab has shown encouraging results; however, long-term follow-up data are not available. These investigators performed a retrospective analysis of 37 patients (25 boys) with steroid-dependent nephrotic syndrome who were treated with rituximab (375 mg/m(2) given weekly for 1 to 4 courses). Long-term follow-up data (greater than 2 years, median of 36 months, range of 24 to 92.8) are available for 29 patients (12 boys). Twenty-six of 37 (70.3 %) patients remained in remission after 12 months. Relapses occurred in 24 (64.8 %) patients after a median of 9.6 (range of 5.2 to 64.1) months. Time to first relapse was significantly shorter in patients receiving 1 or 2 compared to 3 or 4 initial infusions. In the 29 patients with long-term follow-up for greater than 2 years, 12 (41 %) patients remained in remission after the initial rituximab course for greater than 24 months, 7 (24.1 %) patients without further maintenance immunosuppression. Nineteen children received 2 to 4 repeated courses of rituximab increasing the total number of patients with long-term remission to 20 (69 %), remission including 14 (48 %) patients off immunosuppression. The proportion of patients with long-term remission was not related to the number of initial rituximab applications. No serious side effects were noted. The authors concluded that rituximab is an effective treatment option in the short- and long-term control of
treatment refractory SSNS. Moreover, they state that further controlled studies are needed to address optimal patient selection, dose and safety of rituximab infusions.

UpToDate reviews on “Treatment protocols for multiple myeloma” (Brenner et al, 2013), “Treatment of relapsed or refractory multiple myeloma” (Rajkumar, 2013a), “Determination of initial therapy in patients with multiple myeloma” (Rajkumar, 2013b), and “Treatment of kidney disease in multiple myeloma” (Rajkumar et al, 2013) do not mention the use of rituximab (Rituxan). Also, the 2012 NCCN Drugs and Biologics Compendium does not list other forms of multiple myeloma as a recommended indication of rituximab.

An UpToDate review on “Plasma cell leukemia” (Rajkumar, 2013) states that “There have been no prospective randomized trials investigating the treatment of PCL. Recommendations are primarily based upon data from small retrospective series, case reports, and extrapolation of data from patients with multiple myeloma. In general, patients younger than 65 in good performance status are treated with aggressive induction therapy, such as VDT-PACE (bortezomib, dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, and etoposide) followed by hematopoietic cell transplantation (HCT) …. Chemotherapy alone is the principal option for those ineligible for HCT”. Rituximab is not mentioned as a therapeutic option. Also, the 2012 NCCN Drugs & Biologics Compendium on rituximab does not list plasma cell leukemia as a recommended indication.

In a Cochrane review, Lunn and Nobile-Orazio (2012) assessed the effects of immunotherapy for IgM anti-myelin-associated glycoprotein paraprotein-associated demyelinating peripheral neuropathy. These investigators searched the Cochrane Neuromuscular Disease Group Specialized Register 6 June 2011), CENTRAL (2011, Issue 2), MEDLINE (January 1966 to May 2011) and EMBASE (January 1980 to May 2011) for controlled trials. They also checked bibliographies and contacted authors and experts in the field. They included randomized or quasi-randomized controlled trials involving participants of any age treated with any type of immunotherapy for anti-myelin-associated glycoprotein antibody-associated demyelinating peripheral neuropathy with monoclonal gammopathy of undetermined significance and of any severity. The primary outcome measure was change in the Neuropathy Impairment Scale or Modified Rankin Scale at six months after randomization. Secondary outcome measures were: Neuropathy Impairment Scale or the Modified Rankin Score at 12 months after randomization; 10-meter walk time, subjective clinical scores and electrophysiological parameters at 6 and 12 months after randomization; IgM paraprotein levels and anti-myelin-associated glycoprotein antibody titers at six months after randomization; and adverse effects of treatments. The 2 authors independently selected studies. Two authors independently assessed the risk of bias in included studies. They identified 7 eligible trials (182 participants), which tested intravenous immunoglobulin, alfa interferon alfa-2a, plasma exchange, cyclophosphamide and steroids, and rituximab. Only two trials, of intravenous immunoglobulin (with 33 participants, including 20 with antibodies against myelin-associated glycoprotein), had comparable interventions and outcomes, but both were short-term trials. There were no clinical or statistically significant benefits of the treatments used on the outcomes predefined for this review, but not all the predefined outcomes were used in every included trial. Intravenous immunoglobulin showed a statistical benefit in terms of improvement in Modified Rankin Scale at 2 weeks and 10-meter walk time at 4 weeks. Cyclophosphamide failed to show any benefit in the trial’s primary outcome, and showed a barely significant benefit in the primary outcome specified here, but some toxic adverse events were identified. A trial of rituximab was of poor methodological quality with a high-risk of bias and a further larger study is awaited. Serious adverse events were few in the other trials. The authors concluded that there is inadequate reliable evidence from trials of immunotherapies in anti-myelin-associated glycoprotein paraproteinemic neuropathy to form an evidence base supporting any particular immunotherapy treatment. There is very low quality evidence of benefit from rituximab. Large well-designed randomized trials of at least 6 to 12 months duration are required to assess existing or novel therapies, preferably employing unified, consistent, well-designed, responsive and valid outcome measures.

Also, an UpToDate review on “Clinical course and management of monoclonal gammopathy of undetermined significance” (Rajkumar, 2013) does not mention the use of rituximab as a therapeutic option.

There is limited evidence for the use of rituximab as a last resort (third line) treatment of chronic cutaneous or musculoskeletal graft versus host disease. Available clinical trial evidence is limited to small, uncontrolled, phase II studies with limited follow-up. In addition, McIver et al (2010) also found...
that administration of rituximab early after T cell-deplete SCT is associated with prolonged profound and life-threatening cytopenias, and should be avoided.

The anti-CD20 monoclonal antibody rituximab produced a clinical response rate of 70% mainly for musculoskeletal and cutaneous chronic GVHD (Cutler et al, 2006). These responses were durable through 1 year after initiation of therapy and allowed a 75% reduction in steroid doses.

A review on immunosuppressive agents for graft versus host disease in UpToDate commented: “Prospective studies are investigating the use of the anti-CD20 monoclonal antibody, rituximab, in an attempt to decrease allogeneic donor B cell immunity and, potentially, associated chronic GVHD. While initial results demonstrate decreased B cell immunity and low rates of chronic GVHD, this approach remains experimental. Randomized trials are needed to determine the efficacy and toxicity of rituximab in this setting, including the effect on long-term B cell function.”

British Society of Haematology guidelines on acute graft versus host disease recommends against the use of rituximab. British Society of Haematology guidelines on chronic graft versus host disease suggest rituximab as a second line treatment option in refractory cutaneous or musculoskeletal chronic graft versus host disease. This is a weak recommendation based upon moderate quality evidence (2B).

Current guidelines (Costanzo et al, 2010) recommend the use of rituximab for antibody mediated rejection in heart transplant recipients, with steroids, plasmapheresis and/or IVIG, to reduce the risk of recurrent rejection. Initial therapy of antibody-mediated rejection can include immunoadsorption and corticosteroid or plasmapheresis/low dose of IVIG and corticosteroid. The guidelines state that rituximab can be added to reduce the risk of recurrent rejection. Changes in therapy, which can be considered for maintenance immunosuppression in patients who experience antibody mediated rejection, can include switch to tacrolimus in patients receiving cyclosporine-based immunosuppression, increased doses of mycophenolate mofetil, and corticosteroids.

National Comprehensive Cancer Network’s Drugs & Biologics Compendium lists acute lymphoblastic leukemia (ALL) as a recommended (2A recommendation) indication of rituximab -- induction/consolidation therapy for Philadelphia chromosome-negative ALL for patients aged greater than or equal to 40 years as a component of HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) regimen alternating with high-dose methotrexate and cytarabine with rituximab.

Sauvaget et al (2012) reported the case of a 6-year old boy who had Kawasaki disease resistant to intravenous immunoglobulin and systemic steroids. Because of an uncontrolled disease course, with significant lesions of the coronary arteries, anti-CD20 treatment was used. Rapid clinical, biological, and cardiac improvement was observed. The patient tolerated the treatment well. Also, an UpToDate review on “Treatment of refractory Kawasaki disease” (Sundel, 2013) states that “New antiinflammatory agents, including biologic response modifiers, become available regularly. Rituximab, a B cell depleting monoclonal anti-CD20 antibody, was reported effective in a single case involving a child with KD refractory to IVIG and glucocorticoids”.

Leger et al (2013) examined if rituximab 375 mg/m2 was efficacious in patients with immunoglobulin M (IgM) anti-myelin-associated glycoprotein antibody demyelinating neuropathy (IgM anti-MAG demyelinating neuropathy). A total of 44 patients with IgM anti-MAG demyelinating neuropathy were enrolled in this randomized, double-blind, placebo-controlled trial. The inclusion criteria were inflammatory neuropathy cause and treatment (INCAT) sensory score (ISS) greater than or equal to 4 and VAS greater than 4 or ataxia score greater than or equal to 2. The primary outcome was mean change in ISS at 12 months. Twenty-six patients were randomized to a group receiving 4 weekly infusions of 375 mg/m2 rituximab, and 28 patients to placebo. Intention-to-treat analysis, with imputation of missing ISS values by the last observation carried forward method, showed a lack of mean change in ISS at 12 months, 1.0 ± 2.7 in the rituximab group, and 1.0 ± 2.8 in the placebo group. However, changes were observed, in per-protocol analysis at 12 months, for the number of patients with an improvement of at least 2 points in the INCAT disability scale (p = 0.027), the self-evaluation scale (p = 0.016), and 2 subscores of the Short Form-36 questionnaire. The authors concluded that although primary outcome measures provided no evidence to support the use of rituximab in IgM anti-MAG demyelinating neuropathy, there were improvements in several secondary outcomes in per-protocol analysis. This study provided Class I evidence that rituximab is ineffective in improving ISS in patients with IgM anti-MAG demyelinating neuropathy.
An UpToDate review on "Extrinsic nonimmune hemolytic anemia due to mechanical damage: Fragmentation hemolysis and hypersplenism" (Schrier, 2013) does NOT mention the use of rituximab as a therapeutic option.

Miya et al (2014) noted that the NNMDAR is involved in normal physiological and pathological states in the brain. Anti-NMDAR encephalitis is characterized by memory deficits, seizures, confusion, and psychological disturbances in males and females of all ages. This type of encephalitis is often associated with ovarian teratoma in young women, but children are less likely to have tumors. Anti-NMDAR encephalitis is a neuroimmune syndrome in patients with autoantibodies recognizing extracellular epitopes of NMDAR, and the autoantibodies attenuate NMDAR function through the internalization of NMDAR. Following the initial symptoms of inflammation, the patients show the various symptoms such as memory loss, confusion, emotional disturbances, psychosis, dyskinesia, decrease in speech intelligibility, and seizures. About 50 % of these patients improved with immunotherapy including high-dose intravenous corticosteroids and IVIG is administrated to these patients, but the patients who had no improvement with these therapies require further treatments with rituximab or cyclophosphamide. It is necessary to detect anti-NMDAR antibodies at early stages, because the prognosis of these patients may be improved by early treatment. Recovery is slow, and the patients may have some disturbances in their motor function and cognition. The authors concluded that the pathologic mechanism underlying the development of anti-NMDAR encephalitis has been elucidated gradually, but the optimal treatment has not yet been clarified. They stated that further studies are required to clarify in detail the mechanism underlying anti-NMDA encephalitis and to develop effective treatments.

In a multi-center retrospective study, Dale et al (2014) evaluated the utility and safety of rituximab in pediatric autoimmune and inflammatory disorders of the CNS. A total of 144 children and adolescents (median age of 8 years, range of 0.7 to 17; 103 female) with NMDA receptor (NMDAR) encephalitis (n = 39), opoclonus myoclonus ataxia syndrome (n = 32), neuromyelitis optica spectrum disorders (n = 20), neuropsychiatric systemic lupus erythematosus (n = 18), and other neuroinflammatory disorders (n = 35) were studied. Rituximab was given after a median duration of disease of 0.5 years (range of 0.05 to 9.5 years). Infusion adverse events were recorded in 18/144 (12.5 %), including grade 4 (anaphylaxis) in 3. Eleven patients (7.6 %) had an infectious adverse event (AE), including 2 with grade 5 (death) and 2 with grade 4 (disabling) infectious AE (median follow-up of 1.65 years [range of 0.1 to 8.5]). No patients developed progressive multifocal leukoencephalopathy. A definite, probable, or possible benefit was reported in 125 of 144 (87 %) patients. A total of 17.4 % of patients had a modified Rankin Scale (mRS) score of 0 to 2 at rituximab initiation, compared to 73.9 % at outcome. The change in mRS 0 to 2 was greater in patients given rituximab early in their disease course compared to those treated later. The authors concluded that while limited by the retrospective nature of this analysis, these findings supported an off-label use of rituximab, although the significant risk of infectious complications suggested rituximab should be restricted to disorders with significant morbidity and mortality. This study provides Class IV evidence that in pediatric autoimmune and inflammatory CNS disorders, rituximab improves neurologic outcomes with a 7.6 % risk of adverse infections.

Ikeguchi et al (2012) reported the case of a young woman with anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis, without tumor, who was successfully treated with rituximab. Because conventional immunotherapy, including corticosteroids, immunoglobulin (IVIG), and plasma exchange showed little improvement in this patient, these researchers introduced another treatment using rituximab. A week after the first administration of rituximab, her symptoms improved gradually and significantly. The authors concluded that this case provided in-vivo evidence that rituximab is an effective agent for treating anti-NMDAR encephalitis, even in those cases where conventional immunotherapies have been ineffective. They stated that rituximab should be regarded as a beneficial therapeutic agent for this disease. This is a single case study.

In a multi-institutional observational study, Titulaer et al (2013) tested for the presence of NMDAR antibodies in serum or CSF samples of patients with encephalitis between Jan 1, 2007, and Jan 1, 2012. All patients who tested positive for NMDAR antibodies were included in the study; patients were assessed at symptom onset and at months 4, 8, 12, 18, and 24, by use of the modified Rankin scale (mRS). Treatment included first-line immunotherapy (steroids, IVIG, plasmapheresis), second-line immunotherapy (rituximab, cyclophosphamide), and tumor removal. Predictors of outcome were determined at the Universities of Pennsylvania and Barcelona (Spain) by use of a generalized linear mixed model with binary distribution. These researchers enrolled 577 patients (median age of 21 years, range of 8 months to 85 years; 211 of whom were children (less than 18 years). Treatment effects and
outcome were assessable in 501 (median follow-up of 24 months, range of 4 to 186): 472 (94 %) underwent first-line immunotherapy or tumor removal, resulting in improvement within 4 weeks in 251 (53 %). Of 221 patients who did not improve with first-line treatment, 125 (57 %) received second-line immunotherapy that resulted in a better outcome (mRS 0-2) than those who did not (odds ratio [OR] 2.69, CI: 1.24 to 5.80; p = 0.012). During the first 24 months, 394 of 501 patients achieved a good outcome (mRS 0-2; median 6 months, IQR 2 to 12) and 30 died. At 24 months’ follow-up, 203 (81 %) of 252 patients had good outcome. Outcomes continued to improve for up to 18 months after symptom onset. Predictors of good outcome were early treatment (0.62, 0.50 to 0.76; p < 0.0001) and no admission to an intensive care unit (0.12, 0.06 to 0.22; p < 0.0001). Moreover, 45 patients had one or multiple relapses (representing a 12 % risk within 2 years); 46 (67 %) of 69 relapses were less severe than initial episodes (p < 0.0001). In 177 children, predictors of good outcome and the magnitude of effect of second-line immunotherapy were similar to those of the entire cohort. The authors concluded that most patients with anti-NMDAR encephalitis respond to immunotherapy. Second-line immunotherapy is usually effective when first-line treatments fail. In this cohort, the recovery of some patients took up to 18 months. It is unclear how many patients received rituximab as 2nd line therapy in this observational study. The main drawback of the study by Titulaer et al (2013) was that the study was not randomized, but it is precursory to future trials to establish the efficacy of each individual treatment (e.g., steroids, intravenous immunoglobulins, plasmapheresis, rituximab, and cyclophosphamide) and duration of immunotherapy.

Hachiya et al (2013) measured anti- NMDAR autoantibody levels and assessed B cell subsets using multi-color flow cytometry of peripheral blood mononuclear cells (PBMCs) from a recurrent anti-NMDAR encephalitis case to evaluate the effectiveness of rituximab treatment. Rituximab depleted CD20(+) fractions of naïve and memory B cell subsets and reduced the number of CD20(-) plasmablasts. The authors concluded that the findings of this study suggested that short-lived plasmablasts are removed by rituximab-induced depletion of the CD20(+) B cell population. Increased numbers of plasmablasts in PBMCs may be a candidate predictive factor for unfavorable prognosis of anti-NMDAR encephalitis and an indication of when to commence second-line immunotherapy. This was an in-vitro study.

Brown et al (2014) stated that autoimmune encephalitis associated with antibodies to leucine-rich glioma inactivated 1 (LG1) is recently described and there is a lack of detailed reports on the treatment of relapsing or refractory cases and long-term outcomes. Two case reports were presented. Both cases had facio-brachial dystonic seizures (FBDS) and received rituximab after relapsing or refractory disease. Both cases achieved sustained clinical remission of up to 15 and 56 months, respectively. Rituximab use allowed withdrawal of corticosteroids and was well-tolerated. The authors concluded that randomized clinical trials are needed in LG1 encephalitis and other autoimmune encephalitides.

In an observational study, Irani et al (2014) described the safety and effectiveness of rituximab in 5 patients with voltage-gated potassium channel (VGKC)-complex/leucine-rich, glioma-inactivated 1 (LG1) antibody-associated encephalopathy. This case series reported sequential seizure frequencies, modified Rankin Scale scores, and VGKC-complex antibody titers in 5 adult patients (median age of 65 years; range of 48 to 73 years) treated with rituximab. Median time from symptom onset to rituximab initiation was 414 days (range of 312 to 851 days). One patient showed a rapid clinical improvement after treatment with rituximab alone and experienced a rituximab-responsive clinical relapse. Another showed possible improvement on neuropsychometric memory indexes after rituximab therapy. In contrast, all patients showed robust responses to treatment with glucocorticoids, intravenous immunoglobulins, and/or plasma exchange at some point in their illness. Treatment with glucocorticoids-less so with intravenous immunoglobulins and plasma exchange-was associated with the most marked reductions in VGKC-complex antibodies. The only patient who did not receive glucocorticoids showed the poorest clinical and serologic responses. The authors concluded that rituximab was well-tolerated in this predominantly older adult patient population and may be an effective option for some patients with LG1 antibody-associated encephalopathy. They stated that glucocorticoid therapy appears particularly efficacious; earlier rituximab administration and randomized trials are needed to formally evaluate effectiveness.

Benitah et al (2011) noted that Behcet's disease (BD) is a multi-system inflammatory disorder of uncertain etiology with a variety of potential manifestations throughout the body, and its ocular complications are some of its most devastating. Treatment with immunosuppressive agents has improved outcomes, but many patients suffer from disease that responds poorly to conventional therapies. Because of this, therapy with a variety of biological response modifiers has been employed. The earliest was interferon-alpha, and a multitude of reports have described its benefits for the uveitis
associated with BD. Many patients enjoy durable remissions of their ocular inflammatory disease even after discontinuation of therapy, but side-effects are almost universal and some can be dangerous. Of the newer biological response modifiers, infliximab, a monoclonal antibody to TNF-alpha, has been most extensively studied. It is reported to be rapidly effective in many cases of BD uveitis, though with conflicting data as to the ability to induce durable remission after cessation of treatment. Side-effects are relatively rare, but may be serious. Several reports have been published on the use of other biologic agents, including adalimumab, etanercept, and rituximab. Of the 3 of these, adalimumab has the most promising initial evidence, etanercept has very few positive reports in patients with BD uveitis (and is likely ineffective in uveitis in general), and rituximab is lacking data. The authors concluded that although RCTs are almost completely lacking, currently available evidence is promising that biologic agents can prove an invaluable addition to the armamentarium of the practitioner treating patients with BD uveitis.

Lin et al (2013) stated that progressive familial intrahepatic cholestasis type 2 (PFIC2) results from recessive mutations in the adenosine triphosphate-binding cassette B11 gene, which encodes for bile salt export pump (BSEP). Liver transplantation (LT) is offered to PFIC2 patients with end-stage liver disease. Reports have described recurrent cholestasis in PFIC2 patients after transplantation, and this has been associated with immunoglobulin G antibodies to BSEP. High-titer anti-BSEP antibodies appeared to correlate with episodes of cholestatic graft dysfunction. There is no established paradigm for treating antibody-mediated post-transplant BSEP disease. It appeared to be refractory to changes in immunosuppressant medications that would typically be effective in treating allograft rejection. Taking what is known about its pathophysiology, these researchers designed a treatment consisting of rituximab in combination with intravenous immunoglobulin (IVIG) and plasmapheresis. Using this approach, the authors reported the successful management of 2 patients with antibody-mediated recurrence of PFIC2 after LT. The main drawback of this study was its limited sample size (n = 2). Furthermore, the findings were confounded by the combinational use of rituximab, IVIG, and plasmapheresis.

The largest trial of rituximab in inflammatory myositis, the Rituximab in Myositis (RIM) trial, involved 195 patients, all of whom were treated with rituximab either at baseline or after an 8-week delay, including 76 patients with adult DM and polymyositis (PM) and 48 patients with juvenile DM; all patients had disease refractory to glucocorticoids and at least 1 immunosuppressive or immunomodulatory agent (mean of 3.1 agents in addition to the glucocorticoid) (Oddis et al, 2013). No differences in response to rituximab were seen between the 2 groups to which the patients were allocated. Patients were randomly assigned to receive rituximab (750 mg/m2 up to 1 g, administered intravenously once-weekly for 2 weeks) either on weeks zero and 1 (“early arm”) or on weeks 8 and 9 (“late arm”), and were assigned to receive placebo at the time-point during which they did not receive rituximab. There were no differences between the early and late treatment arms in the time from baseline to achieve the composite response criteria (both at about 20 weeks) or 20 % improvement in strength, nor were there differences between the 2 arms in the frequency with which the response criteria or 20 % improvement in strength were achieved or in the rate of glucocorticoid taper. The disease groups (DM, PM, and juvenile DM) did not differ in outcome. Despite the failure to demonstrate differences based upon the 8-week treatment delay, results of secondary end-points suggested potential benefit, indicating the need for further study. The composite response criterion was achieved by 83 % of the patients receiving rituximab during the 44-week trial, and the mean dose of prednisone in the 160 patients on it at baseline was significantly reduced, from 20.8 to 14.4 mg daily. Response criteria were also met after a second course of therapy by 8 of 9 patients eligible for re-treatment after an initial response and later recurrence; 26 serious adverse effects attributed to the rituximab were observed, most of which were infections. These included pneumonia and cellulitis (6 patients each), as well as urosepsis and herpes zoster (2 patients each), and 1 patient each had septic arthritis, histoplasmosis, urinary tract infection, respiratory failure, heart failure, dysrhythmia, venous thrombosis, syncope, rash, and neurologic symptoms. One patient withdrew from the trial due to adverse effects, and 1 patient died during the trial from a suspected malignancy and stroke. Infusion reactions were more common with the administration of rituximab compared with placebo (15.4 versus 5.3 %).

An accompanying editorial (de Visser et al, 2013) stated that several reasons may explain why the RIM Study failed to achieve its primary efficacy end-point. The investigators mention the following issues: (i) the power calculation based on the postulated effect of rituximab by 8 weeks, (ii) the selection of a placebo phase of 8 weeks, and (iii) the core set of measures and the definition of improvement.

Rider and colleagues (2014) evaluated changes in myositis core set measures and ancillary clinical and laboratory data from the NIH’s subset of patients enrolled in the RIM trial. A total of 18 patients (5 dermatomyositis, 8 polymyositis, 5 juvenile dermatomyositis) completed more in-depth testing of muscle
strength and cutaneous assessments, patient-reported outcomes, and laboratory tests before and after administration of rituximab. Percentage change in individual measures and in the definitions of improvement (DOIs) and standardized response means were examined over 44 weeks. Core set activity measures improved by 18 to 70 % from weeks 0 to 44 and were sensitive to change; 15 patients met the DOI at week 44, 9 patients met a DOI 50 % response, and 4 met a DOI 70 % response. Muscle strength and function measures were more sensitive to change than cutaneous assessments. Constitutional, gastro-intestinal, and pulmonary systems improved 44 to 70 %. Patient-reported outcomes improved up to 28 %. CD20+ B cells were depleted in the periphery, but B cell depletion was not associated with clinical improvement at week 16. The authors concluded that this subset of patients had high rates of clinical response to rituximab, similar to patients in the overall trial. Most measures were responsive, and muscle strength had a greater degree of change than cutaneous assessments. Several novel assessment tools, including measures of strength and function, extra-muscular organ activity, fatigue, and health-related quality of life, are promising for use in future myositis trials. The authors stated that further study of B cell-depleting therapies in myositis, particularly in treatment-naïve patients, is warranted.

Brown et al (2014) stated that autoimmune encephalitis associated with antibodies to leucine-rich glioma inactivated 1 (LGI1) is recently described and there is a lack of detailed reports on the treatment of relapsing or refractory cases and long-term outcomes. Two case reports were presented. Both cases had facio-brachial dystonic seizures (FBDS) and received rituximab after relapsing or refractory disease. Both cases achieved sustained clinical remission of up to 15 and 56 months, respectively. Rituximab use allowed withdrawal of corticosteroids and was well-tolerated. The authors concluded that randomized clinical trials are needed in LGI1 encephalitis and other autoimmune encephalitides.

The NCCN’s clinical practice guideline on “Hodgkin lymphoma” (Version 2.2014) states that “Rituximab should be considered with all 2nd-line chemotherapy regimens for relapsed or refractory NLPHL [nodular lymphocyte-predominant Hodgkin lymphoma]”.

Rodriguez-Porcel et al (2014) stated that acute disseminated encephalomyelitis (ADEM) is characterized by its rapid progression with variable symptoms and severity in adults and children. Multiple therapeutic options have been proposed, but solid evidence is yet to be gathered. These researchers described an adult man with a fulminant form of ADEM unresponsive to numerous treatment modalities. Furthermore, an UpToDate review on “Acute disseminated encephalomyelitis in adults” (Waldman and Jacobs, 2015) does not mention rituximab as a therapeutic option.

An UpToDate review on “Diagnosis and treatment of vitamin B12 and folate deficiency” (Schrier, 2015) does not mention rituximab as a therapeutic option.

UpToDate reviews on “Prevention and management of complex regional pain syndrome in adults” (Abdi, 2015) and “Complex regional pain syndrome in children” (Sherry, 2015) do not mention rituximab as a therapeutic option.

An UpToDate review on “Clinical course and management of monoclonal gammopathy of undetermined significance” (Rajkumar, 2015) does not mention the use of rituximab as a therapeutic option.

Pandey et al (2014) reported on the case of a 45-year old woman with pulmonary sarcoidosis diagnosed 5 years previously; she was on treatment with prednisone and methotrexate for 1 year, developed partial seizure with secondary generalization. MRI showed 3 non-cavitary enhancing lesions in the cerebello-occipital region. These lesions were presumed to be neurosarcoidosis. Methotrexate was discontinued, prednisone dose was increased and azathiopurine and levetiracetam were added. While the patient was on treatment, follow-up imaging showed enlarging brain lesions. Biopsy of the lesions showed Epstein Barr virus (EBV) positive diffuse B cell lymphoma. Immunosuppressants were tapered off and she started on rituximab. Because of lack of improvement after 4 cycles of rituximab, she was then treated with high-dose methotrexate and temozolomide.

An UpToDate review on “Infliximab (Remicade) is a chimeric human-murine antihuman antibody that specifically blocks the effect of tumor necrosis factor-alpha (TNF-alpha). Preliminary results indicate that infliximab may be useful in selected patients with pulmonary and extrapulmonary sarcoidosis refractory to corticosteroid therapy. In one series of seven patients with corticosteroid-refractory neurosarcoidosis, treatment with infliximab (with mycophenolate mofetil in six patients) was associated with symptom relief, regression of neurologic deficits, and a decrease in disease activity on MRI. Another series reported stabilization and improvement in four patients with central nervous system manifestations of
neurosarcoidosis. A single case report describes the successful use of rituximab (monoclonal antibody directed against B cells) in a patient with CNS neurosarcoidosis. Use of infliximab requires an intravenous infusion (5 mg/kg of ideal body weight) initially, and periodically thereafter as the clinical course is monitored”.

In a prospective, dose-ranging, randomized, double-masked phase I/II clinical trial, Suhler et al (2014) examined if rituximab is effective in the treatment of refractory non-infectious scleritis. A total of 12 patients with non-infectious scleritis refractory to systemic corticosteroid and greater than or equal to 1 other systemic immunosuppressive agents were enrolled from January 2007 to March 2010. Subjects were randomly assigned to 500 (n = 5) or 1,000 mg (n = 7) dosing arms of rituximab intravenous infusions (500 or 1,000 mg), given at study days 1 and 15. Initial responders with breakthrough inflammation after study week 24 were offered treatment with an additional cycle of 2 open-label rituximab 1,000 mg infusions. Primary outcomes were reduction of inflammation, as measured with a validated scleritis disease grading scale (SGS) and reduction in corticosteroid dose by greater than or equal to 50 %. Patients were characterized as responders to study therapy if greater than or equal to 1 of these end-points showed improvement and neither showed evidence of worsening. Secondary outcomes were improvement in visual acuity, reduction in pain, and improvement in patient and physician-reported global health assessment. Of 12 enrolled patients, 9 met the SGS end-point at or before week 24, and 4 additionally were able to reduce corticosteroid dose by greater than or equal to 50 %. With regard to secondary outcome measures, 11 and 9 patients showed improvement in patient and physician global health scores, respectively, and 7 patients had reduction in pain. Of 9 initial responders, 7 experienced breakthrough inflammation after 24 weeks and were treated with a second cycle of rituximab infusions. Four patients had significant objective or subjective worsening within 8 weeks of receiving rituximab; this event was averted in subsequent patients by treatment with peri-infusional oral corticosteroid. No other significant adverse events were noted. No differences in efficacy, toxicity, or likelihood of re-treatment were noted between the dosing arms. The authors concluded that rituximab was effective treatment for 9 of 12 enrolled patients with refractory, non-infectious scleritis at 24 weeks, although 7 required re-infusion with rituximab to maintain inflammatory control. The treatment was well-tolerated, and peri-infusional inflammatory exacerbations were managed successfully with oral corticosteroids. They stated that further long-term studies are needed to determine the safety and effectiveness of rituximab in treating non-infectious scleritis and other ocular inflammatory diseases.

An UpToDate review on “Autoimmune pancreatitis” (Greenberger, 2015) states that “Immunomodulatory drugs have been used in patients who fail steroids, relapse, or cannot be weaned off steroids. Successful treatment with rituximab, a monoclonal antibody, has also been reported. However, further studies are required before rituximab can be routinely recommended”.

An UpToDate review on “Juvenile xanthogranuloma” (Puttgen, 2015) does not mention rituximab as a therapeutic option.

Appendix

According to the FDA-approved labeling for Rituxan (2013), rituximab for rheumatoid arthritis is given as two 1,000-mg IV infusions separated by 2 weeks. The labeling states that additional courses of treatment should not occur more frequently than every 16 to 24 weeks. Glucocorticoids administered as methylprednisolone 100 mg IV or its equivalent 30 minutes prior to each infusion are recommended to reduce the incidence and severity of infusion reactions.

According to the FDA-approved labeling, the dose of rituximab for non-Hodgkin’s lymphoma is 375 mg/m2.

The Rituximab labeling states that the dose for chronic lymphocytic leukemia is 375 mg/m2 in the first cycle and 500 mg/m2 in cycles 2-6, in combination with with fludarabine and cyclophosphamide, administered every 28 days.

The labeling states that the dose as a component of Zevalin (ibritumomab tiuxetan) Therapeutic Regimen is 250 mg/m2.

The FDA-labeled dose for Wegener’s granulomatosis and microscopic polyangiitis in combination with glucocorticoids is 375 mg/m2 once weekly for 4 weeks.

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Generic Name</th>
<th>FDA Labeled Indications</th>
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05/06/2015
<table>
<thead>
<tr>
<th>Brand Name</th>
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<tr>
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<td>Secukinumab</td>
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<tr>
<td>Xeljanz</td>
<td>tofacitinib</td>
<td>Rheumatoid arthritis</td>
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</table>

**CPT Codes / HCPCS Codes / ICD-9 Codes**

**CPT codes not covered for indications listed in the CPB:**

83520 Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, not otherwise specified [anti-chimeric antibody testing and/or chimeric anti-TNF antibody testing for Rituxan therapy]

**Other CPT codes related to the CPB:**

96401 - 96450 Chemotherapy administration

**HCPCS codes covered if selection criteria are met:**

J9310 Injection, rituximab, 100 mg

**ICD-9 codes covered if selection criteria are met:**

200.00 - 200.88 Lymphosarcoma and reticulosarcoma and other specified malignant tumors of lymphatic tissue [non-Hodgkin's lymphoma]

201.40 - 201.48 Lymphocytic-histiocytic predominance

202.00 - 202.08 Nodular lymphoma

202.40 - 202.48 Leukemic reticuloendotheliosis

202.80 - 202.88 Other lymphomas

204.00 - 204.01 Acute lymphoid leukemia[Philadelphia chromosome-negative]

204.10 - 204.12 Chronic lymphoid leukemia [CD20-positive]

238.77 Post-transplant lymphoproliferative disorder (PTLD)
273.2  Other paraproteinemias [cryoglobulinemia] [refractory to corticosteroids and other immunosuppressive agents]
273.3  Waldenstrom's macroglobulinemia
279.52 Chronic graft-versus-host disease [last resort treatment]
283.0  Autoimmune hemolytic anemias [refractory]
286.0  Congenital factor VIII disorder
286.1  Congenital factor IX disorder
286.2  Congenital factor XI disorder
286.4  Von Willebrand's disease
286.52 Acquired hemophilia
287.31 Immune thrombocytopenic purpura [refractory]
341.0  Neuromyelitis optica
379.59 Other irregularities of eye movements [opsoclonus-myoclonus-ataxia associated with neuroblastoma]
446.0  Polyarteritis nodosa
446.4  Wegener's granulomatosis
446.6  Thrombotic microangiopathy [refractory thrombotic thrombocytopenic purpura]
580.4  Acute glomerulonephritis with lesion of rapidly progressive glomerulonephritis [pauci-immune glomerulonephritis]
694.4  Pemphigus [corticosteroid-refractory]
694.5  Pemphigoid
694.60 - 694.61 Benign mucous membrane pemphigoid [cicatrical pemphigoid]
694.8  Other specified bullous dermatosis [epidermolysis bullosa acquisita]
710.2  Sjögren syndrome [Sjögren syndrome refractory to corticosteroids and other immunosuppressive agents]
714.0 - 714.2 Rheumatoid arthritis and other inflammatory polyarthropathies [in combination with methotrexate to reduce signs and symptoms and to slow the progression of structure damage in adult patients with moderate-to severely- active RA who have had an inadequate response to one or more tumor necrosis factor (TNF) antagonist therapies [if the member has a contraindication, intolerance or incomplete response to at least 2 of the least cost brands of targeted immune modulators]
996.83 Complications of transplanted heart [antibody mediated rejection in heart transplant recipients]
V42.0  Organ or tissue replaced by transplant, kidney [prophylaxis of rejection in sensitized kidney transplant recipients with donor specific antibodies]

ICD-9 codes not covered for indications listed in the CPB (not all-inclusive):
135  Sarcoidosis
140.0 - 199.2, Neoplasms other than chronic lymphocytic leukemia, non-Hodgkin's lymphoma, or relapsed or refractory hairy cell leukemia including myelodysplastic syndrome
200.00 - 200.08,
200.52 - 200.68, 201.00 - 210.28, 201.50 - 201.99, 202.10 - 202.38, 202.50 - 202.78, 202.90 - 203.82, 204.02, 204.11, 204.20 - 238.76, 238.79 - 239.9

242.00 - 242.01 Toxic diffuse goiter [Graves' ophthalmopathy] [thyroid-associated ophthalmopathy]

245.2 Chronic lymphocytic thyroiditis [Hashimoto's encephalitis]

258.1 Other combinations of endocrine dysfunction [autoimmune polyendocrine syndrome type 1]

273.2 Other paraproteinemias [cryoglobulinemic vasculitis]

277.89 Other specified disorders of metabolism [Rosai-Dorfman disease] [SHML]

279.50 - 279.51, 279.53 Graft-versus host disease

283.10 - 283.19 Non-autoimmune hemolytic anemia

284.81 Red cell aplasia (acquired) (adult) (with thymoma)

288.09 Other neutropenia [autoimmune]

288.4 Hemophagocytic syndromes [lymphohistiocytosis]

289.81 Primary hypercoagulable state [anti-phospholipid syndrome]

323.0 - 323.9, 341.20 – 341.22 Encephalitis, myelitis, and encephalomyelitis [transverse myelitis] [autoimmune encephalitis]

333.6 Myelopathy in disease classified elsewhere [paraneoplastic]

333.91 Stiff man syndrome

340 Multiple sclerosis

356.0 - 356.9 Hereditary and idiopathic peripheral neuropathy [anti-myelin-associated glycoprotein]

357.81 Chronic inflammatory demyelinating polyneuritis

358.00 - 358.01 Myasthenia gravis

359.81 Critical illness myopathy [necrotizing myopathy]

362.89 Other retinal disorders [autoimmune retinopathy]

363.20 Chorioretinitis, unspecified

364.00 - 364.3 Iridocyclitis [uveitis]

370.52 Diffuse interstitial keratitis [Cogan's syndrome]

437.4 Cerebral arteritis [primary angiitis of the central nervous system]

446.0 Polyarteritis nodosa

446.1 Acute febrile mucocutaneous lymph node syndrome [MCLS] (Kawasaki disease)

446.21 Goodpasture's syndrome
447.6  Arteritis, unspecified [primary angiitis of the central nervous system]
491.8  Other chronic bronchitis [bronchiolitis obliterans]
515   Postinflammatory pulmonary fibrosis [granulomatous lymphocytic interstitial lung disease]
516.31 Idiopathic pulmonary fibrosis
581.0 - 581.9  Nephrotic syndrome
582.1  Chronic glomerulonephritis with lesion of membranous glomerulonephritis
582.2  Chronic glomerulonephritis with lesion of membranoproliferative glomerulonephritis
583.1  Nephritis and nephropathy, not specified as acute or chronic with lesion of membranoproliferative glomerulonephritis
583.2  Nephritis and nephropathy, not specified as acute or chronic with lesion of membranous glomerulonephritis
583.81 Nephritis and nephropathy, not specified as acute or chronic, in diseases classified elsewhere [Lupus]
593.4  Other ureteric obstruction [retroperitoneal fibrosis]
696.0  Psoriatic arthropathy
710.0  Systemic lupus erythematosus [and lupus cerebritis and nephritis]
710.1  Scleroderma
710.3  Dermatomyositis [juvenile]
710.4  Polymyositis
713.1  Arthropathy associated with gastrointestinal conditions other than infections [arthritis associated with inflammatory bowel disease]
714.30 - 714.33 Juvenile chronic polyarthritis
728.19  Other muscular calcification and ossification [polymyositis ossificans]
V58.11 - V58.12 Encounter for antineoplastic chemotherapy and immunotherapy

Other ICD-9 codes related to the CPB:
785.6  Enlargement of lymph nodes [Castleman's disease (angiofollicular lymph node hyperplasia)]
996.81 Complications of transplanted kidney [prophylaxis of rejection in sensitized kidney transplant recipients with donor specific antibodies]

The above policy is based on the following references:


211. Appel GB, Catrann DC. Treatment of primary focal segmental glomerulosclerosis. Last reviewed January 2012. UpToDate inc. Waltham, MA.

212. Falk RJ, Schur PH, Appel GP. Therapy of diffuse or focal proliferative lupus nephritis. Last reviewed January 2012. UpToDate inc. Waltham, MA.


236. Appel GB, Cattran DC. Treatment of primary focal segmental glomerulosclerosis. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed January 2013.


239. Bermas BL, Schur PH, Kaplan AA. Treatment of the antiphospholipid syndrome. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed January 2013.


241. Rajkumar SV. Treatment of relapsed or refractory multiple myeloma. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed January 2013a.

242. Rajkumar SV. Determination of initial therapy in patients with multiple myeloma. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed January 2012b.


244. Rajkumar SV. Plasma cell leukemia. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed January, 2013.

245. Rajkumar SV. Clinical course and management of monoclonal gammopathy of undetermined significance. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed January 2013.


258. Schrier SL. Extrinsic nonimmune hemolytic anemia due to mechanical damage: Fragmentation hemolysis and hypersplenism. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed May 2013.


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