Off-Label Uses of Rituximab in Dermatology

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Abstract

Purpose of Review Rituximab has transformed the treatment of B-cell malignancies and rheumatoid arthritis in the past 2 decades. More recently, this anti-CD20 monoclonal antibody has seen increasing usage in the field of dermatology. This review highlights the evidence supporting its use in several important dermatologic conditions.

Recent Findings Key recent findings include the 2018 FDA approval of rituximab for the treatment of moderate-to-severe pemphigus.

Summary Data from randomized controlled trials have demonstrated the efficacy of rituximab in pemphigus, ANCA-associated vasculitis, and cryoglobulinemic vasculitis. More limited data suggests its use in recalcitrant cases of diseases such as pemphigoid, epidermolysis bullosa acquisita, and dermatomyositis. There is scarce evidence and mixed results for rituximab when studied in cutaneous polyarteritis nodosa and cutaneous lupus erythematosus.

Keywords Rituximab · Pemphigus · Pemphigoid · Epidermolysis · Dermatomyositis · Vasculitis

Introduction

Rituximab is a monoclonal antibody directed against the CD20 antigen found on the surface of B-cells [1]. It has dramatically improved the treatment of several diseases over the past 2 decades and is currently FDA-approved for rheumatoid arthritis (RA), chronic lymphocytic leukemia (CLL), non-Hodgkin's lymphoma (NHL), and more recently for pemphigus vulgaris (PV), granulomatosis with polyangiitis (GPA), and microscopic polyangiitis (MPA) [2]. Notably, emerging evidence showing a more significant role of B-cells in autoimmunity than previously thought has resulted in expanded off-label use of rituximab [3]. These recent findings highlight the exciting potential for the effective use of rituximab in dermatological diseases, of which many are autoimmune in nature. In this review, we will summarize what is currently known about the off-label utility of rituximab in various dermatological diseases.

Mechanism of Action

Rituximab is an IgG1 kappa monoclonal antibody that consists of a human constant (Fc) region that is fused to a murine variable (Fab) region [1]. The variable region binds directly to the CD20 antigen which is exclusively located on the surface of both mature and pre-B lymphocytes [1]. Following this binding, recruitment of immune cells by the Fc portion of rituximab can result in lysis of CD20-positive B-cells via three distinct mechanisms: antibody-dependent cell-mediated cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), or induction of apoptosis [1]. Plasma cells and hematopoietic stem cells which lack CD20 are spared from these effects [4, 5]. Thereby, plasma cell antibody production and cell regeneration from hematopoietic precursors is able to continue [6]. Regeneration of B-cells in the peripheral circulation can occur as quickly as 6–12 months post-treatment, and levels of serum immunoglobulins are not markedly decreased [4, 6–10]. The precursors of plasma cells however are affected, and thus the production of autoantibodies is indirectly inhibited for an extended time [3, 4, 11].

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Due to the fact that rituximab cannot distinguish between normal vs pathological B-cells, the normal B-cell population is totally depleted for several months [12]. As antigen-specific memory B-cells make up only a small percentage of total B-cells [13], measuring total B-cell repletion does not necessarily characterize the autoimmune cell population. In addition to its most widely known mechanism of CD20 + B-cell depletion, rituximab has multiple other described mechanisms of action. It can interfere with several antigens, such as CD40 and CD80 on B-cells, as well as HLA-DR, CD69, inducible costimulator, and CD40L on helper T-cells [14–17]. Disrupting the interaction of B and T-cells through these effects may dampen the impact of these cells in auto-immune processes [18]. Additionally, rituximab can alter the production of several proinflammatory cytokines, namely decreasing TNF-alpha and increasing B-cell activating factor (BAFF) and IL-10. It can also lead to the upregulation of CD86 expression on monocyte and macrophage surfaces [19]. Finally, antibodies directed against CD20 such as rituximab may induce CD4+/CD25+ T_{reg} cells [20–22].

Rituximab's mechanism of action has important implications in clinical management and its utility in the inpatient setting. As rituximab leads to death of B-cells but not plasmablasts or plasma cells, its onset of action is typically slow. As such, urgent administration of rituximab does not offer an immediate clinical benefit. The major benefit is, however, the ultimate ability to taper down corticosteroids more rapidly. For example, in pemphigus, initiation of rituximab allows taper to minimal dose corticosteroids, defined as less than 10 mg per day, between 4 and 6 months, with peak reduction at month 7. As such, delays in the administration of rituximab would ultimately lead to increased time on high-dose steroids, along with their respective toxicity.

Dosage

There are multiple established dosage protocols for rituximab currently in use for several diseases [23]. The first is a 375 mg/m^2 IV infusion once per week for 1–2 months as used for lymphoma [24]. Subcutaneous rituximab utilizing higher concentrations as well as the presence of hyaluronidase have also been approved [25], though its use is primarily in cancer. The next is a two-dose IV administration of 1000 mg each, done 2 weeks apart. This protocol is primarily used in rheumatoid arthritis [26], as well as other autoimmune diseases [27, 28, 29•]. Additionally, anti-CD20 antibodies are occasionally given as intralesional agents (10 mg/mL, 1 mL per lesion administered in several sessions) for cutaneous lymphomas [30], orbital lymphomas [31], and lymphoid hyperplasia [32]. There are various other regimens present in the literature combining rituximab with concurrent usage of other agents as well [33]. Recent retrospective studies have supported the use of additional cycles or maintenance doses, given their association with increased complete remissions [34–37]. Currently, there is no expert consensus on the optimal rituximab dosage and administration for its off-label uses in regards to safety and efficacy [1]. This article will briefly mention specific dosing information for each dermatologic disease covered.

Adverse Events/Complications

Overall, serious adverse events resulting from rituximab treatment are very rare [6]. Infusion reactions are the most common, occurring in over half of patients [3]. These reactions are typically mild and usually occur only with the first infusion [24, 38]. Common symptoms include fevers, chills, rigors, flushing, angioedema, nausea, and vomiting. Such reactions will generally resolve with a slowing of the infusion rate, which can be increased again once the symptoms subside [3]. Serious infusion reactions such as bronchospasm or hypotension can occur in up to 10% of patients. Withholding antihypertensive medication for 12 h prior to the infusion for patients with high blood pressure can be helpful for avoiding the latter [3]. Furthermore, hypersensitivity reactions that occur within minutes after infusion and are usually anaphylactic can occur. Due to this risk, medications such as epinephrine and antihistamines should be kept readily available for immediate treatment of such reactions [3]. Various pre-medication strategies are used without clear consensus and are often infusion-center dependent. We, however, utilize premedication with 40 to 80 mg of methylprednisolone, 50 mg of diphenhydramine, and 1000 mg of acetaminophen as our standard operative procedure.

Perhaps the most concerning acute infusion reaction is the development of a potentially fatal cardiac arrythmia. While this phenomenon is extremely rare, it has been described in the literature, prompting caution in patients with underlying cardiovascular disease. However, it does not appear to be associated with underlying cardiovascular risks [39, 40]. While arrythmia is best described in the lymphoma literature, it has also been described in patients with autoimmune diseases [39]. However, diseases such as rheumatoid arthritis are independently associated with an increased underlying risk of arrythmia [41]. Studies have, however, demonstrated that the addition of rituximab to cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) therapy was not associated with an increase in cardiovascular toxicity, calling into question a significant association [42]. Nevertheless, this risk remains extremely low and to our knowledge has not been shown in patients receiving rituximab for pemphigus vulgaris [43, 44].

The risk of infection is more controversial and disease dependent. Rituximab is contraindicated in patients with

severe active infections or significant immunosuppression. Yet, in some cases, infection risk may remain constant or even decrease relative to treatment with alternative agents, as it may represent a more efficient immunosuppressive strategy in a patient on high-dose steroids and various conventional immunosuppressants [45, 46]. Additionally, caution should be taken when prescribing to those with a history of recurrent infections [3]. One study of RA patients on rituximab found that 35% of the patients in the treatment group developed an infection, while 28% of the placebo group did, and serious infections occurred in 2% of the rituximab patients compared to 1% in the control group [47]. Respiratory and urinary infections were the most common.

Another potential complication of rituximab is the development of human antichimeric antibodies (HACAs), which develop in < 1% of lymphoma patients [48]. The risk may be higher in those being treated for autoimmune diseases, as a study showed that 6/18 lupus patients developed HACAS [49]. However, none of the affected patients had complications due to the development of HACAs. Progressive multifocal leukoencephalopathy (PML) resulting from reactivation of the JC virus is a rare but serious complication that has been reported in a small number of patients [50].

Contraindications

Current contraindications to rituximab therapy include active infections as well as hepatitis B and hepatitis C infections, though the hepatitis C contraindication has proven somewhat controversial as it can be used in hepatitis C-associated cryoglobulinemic vasculitis [51, 52]. The use in HIV has additionally been controversial as there does not appear to be an increased risk of infection in the lymphoma literature [53]. Pregnancy is generally a contraindication to the use of rituximab, though risks of alternative therapies must be considered when weighing treatment decisions [3, 54, 55]. Congestive heart failure (New York Heart Association class IV), prior hypersensitivity reactions, murine protein sensitivity, and severe drug reactions are additional contraindications [53].

Pretreatment Considerations

A detailed history should be taken prior to initiating rituximab therapy, focusing on comorbidities such as pulmonary and heart disease, recurrent infections, and allergies. A comprehensive physical exam can be used to identify possible contraindications, particularly in elderly patients. Patients should receive all indicated vaccines at least 4 weeks prior to beginning treatment. However, due to limited data on live attenuated vaccines in rituximab-treated patients, such vaccines are not currently recommended [53].

Due to the risk of reactivation [56, 57], screening for hepatitis B (HBV) infection should be done. Rituximab is considered highly immunosuppressive, and loss of anti-HBsAb during treatment has been described in detail [58]. Screening for HBsAg, anti-HBc, and anti-HBs can identify patients who require HBV vaccination, as well as chronic HBV patients who will benefit from a multidisciplinary approach with a hepatologist to monitor and help prevent reactivation and associated complications [59]. Anti-viral prophylaxis, such as lamivudine or entecavir, is recommended in such patients and should begin a month prior to rituximab and continue for at least 12 months after the final dose [58, 60]. Close monitoring with HBV DNA and liver function tests for 3–6 months after stopping therapy is also recommended [61].

The risk of hepatitis C (HCV) reactivation is more controversial [51]. There are studies showing HCV reactivation following rituximab therapy, but these are almost exclusively found in the oncology literature where rituximab is often used in chemotherapy regimens alongside hepatotoxic agents [62, 63]. So, although more data is needed to fully elucidate this risk, screening for HCV prior to rituximab is prudent to identify active infections and can help guide the management of the patient.

The American College of Rheumatology recommended in 2008 to screen for tuberculosis prior to initiating rituximab for rheumatoid arthritis [64]. However, multiple studies and an international expert panel indicate that there is no increased risk of TB with rituximab monotherapy in patients with rheumatologic disease, and thus no need for screening [53, 65]. The apparent risk of tuberculosis in RA patients treated with rituximab may have been due to the fact that rituximab is administered with glucocorticoid pulses in RA, which is itself a risk factor for tuberculosis [66]. As it stands, the decision to test screen for TB is not required to initiate rituximab but should be made on an individual basis. Furthermore, the presence of an acquired or inherited immunodeficiency, such as HIV/AIDS, should be investigated in any patients under consideration for rituximab treatment [67]. Finally, since low baseline levels of IgG are an established risk factor for rituximab-associated severe infections, these levels should be determined and continually monitored at each cycle of rituximab [53, 68].

Given that rituximab results in prolonged periods of B-cell depletion and is associated with an increased risk of infectious complications, it is prudent to discuss how rituximab-treated patients are affected by the COVID-19 pandemic. Although data on this topic is still emerging, a large study of nearly 4000 rheumatologic patients found that rituximab was associated with an increased risk of COVID-19-related death when compared to methotrexate monotherapy [69]. A

large retrospective study of AIBD patients from Iran found that the relative risks of both contracting Sars-Cov-2 or being hospitalized from it, each decreased with each passing month since the last dose of rituximab [70]. Additionally, a five-fold increase in the incidence of COVID-19 was identified in AIBD patients who received rituximab [71]. Conversely, a retrospective study of 49 rituximab-treated patients with various conditions showed no significant relationship between anti-CD20 treatment and COVID-19 clinical outcomes including hospitalization and death, regardless of the treatment timing [72]. Interestingly, many patients demonstrated recovery from COVID-19 without a detectable humoral response, indicating that the development of antibodies may not be necessary for recovery from this virus.

The use of preexposure prophylaxis with Evusheld (tixagevimab co-packaged with cilgavimab) has been proposed in immunosuppressed patients, including those treated with rituximab. Evidence-based risk reduction in dermatologic patients on rituximab, however, remains unclear and can be considered on a case-by-case basis. Much more data will be needed to investigate the risk of COVID-19 reactivation, reinfection, and response to vaccines in rituximab-treated patients, and individualized clinical judgment and expertise should be relied upon when treating these complex patients.

Rituximab in Dermatologic Conditions

Pemphigus

The use of rituximab in pemphigus originated from the observation that some lymphoma patients being treated with the drug experienced improvement in associated paraneoplastic pemphigus [4]. Since then, the benefit of rituximab has been documented in more than 450 cases of pemphigus vulgaris (PV), including those with severe disease [4, 5, 9, 11, 12]. While rituximab is approved for use in patients with PV, it remains off-label for other forms of pemphigus. Most of these patients were treated with rituximab as an adjuvant therapy with either the lymphoma protocol (weekly 375 m/m^2 for 4 weeks) or the RA protocol (1000 mg, days 1 and 15). Overall, approximately 85% of patients achieved complete resolution following rituximab. Nearly 70% of these patients had to remain on systemic therapy following treatment, typically at a reduced dose, to maintain resolution [12]. Serious side effects occurred in under 5% of patients. Additionally, patients treated with rituximab had a lower mortality rate than those on conventional therapy [12]. However, an approximate relapse rate of ~50% does leave some unmet need in patients with pemphigus [12]. In 80% of cases, PV and pemphigus foliaceus (PF) patients treated with rituximab showed decreased serum levels of Dsg1/Dsg3-reactive antibodies [73], which is associated

with improved outcomes clinically [67, 74, 75]. In a 2017 large multicenter randomized trial, Joly et al. demonstrated that rituximab alongside short-term prednisone is superior to prednisone monotherapy in treating PV and PF and results in fewer adverse events [29•]. Multiple other studies also show evidence to support the first-line use of rituximab in pemphigus [76, 77]. In 2018, the FDA approved rituximab for the use of moderate-to-severe pemphigus. Several other studies have shown rituximab to be effective in PF and severe childhood PV [6, 78–82]. Paraneoplastic pemphigus also termed paraneoplastic autoimmune multiorgan syndrome, demonstrates a less consistent response to rituximab, presumably due to a more predominant role of T-cells [83].

Pemphigoid

The evidence for rituximab usage in pemphigoid disease is not as robust as that of pemphigus, and leading guidelines only recommend it as a third-line option reserved for refractory bullous pemphigoid (BP) cases [84]. Data from randomized controlled trials is lacking, but several retrospective studies have shown clinical benefits of the drug in these patients.

A retrospective case series from Tovanabutra et al. showed that 29/38 pemphigoid patients achieved complete resolution after a median of one cycle, with 15 of those patients able to remain off therapy. A significant reduction in BP180 antibodies was also observed [85]. Ahmed et al. saw complete clinical resolution in all 12 refractory BP patients studied following rituximab treatment (375 m/m^2 weekly for 8 weeks, then monthly for 4 months) combined with IVIg. It is unclear, however, to what extent this can be attributed to the rituximab versus IVIg. No adverse events were reported, and patients remained in remission at 6-year follow-up [86]. In another study, the combination of rituximab (500 mg weekly for 1 month) and corticosteroids led to a significant clinical improvement and 8/12 patients were in off-therapy remission at 2 years [87]. Furthermore, Polanksy et al. examined 20 patients with severe recalcitrant BP. 15 of the patients experienced complete (7) or partial (8) remission following RA protocol rituximab therapy. BP antibody levels were correlated with this clinical improvement [88]. Several smaller case studies have shown the effectiveness of rituximab, typically in BP patients who did not respond adequately to conventional therapy [89–94]. There is also evidence for the efficacy of rituximab in successfully treating pemphigoid gestationis as well as nivolumab-induced BP [95–98].

A systematic review of the literature in 2019 analyzed 62 BP patients treated with rituximab and found that 85% of patients had complete responses to the drug. A recurrence rate of 29% was identified after a mean of 10.2 months, and adverse events occurred in nearly 25% of patients [99].

There is still controversy regarding rituximab for pemphigoid diseases given less consistent improvement than in pemphigus, as well as the significantly older and more frail patient population [2, 67, 100, 101]. Nonetheless, rituximab certainly has shown clinical benefit and can be an option in recalcitrant BP cases [102].

Mucous membrane pemphigoid (MMP) can often be a difficult disease to treat, and rituximab has been proven to be an effective third-line option in refractory cases [67, 103]. Case series and small cohorts have illustrated the effectiveness of the drug, particularly when combined with IVIg or other traditional treatments [104–109]. Both the RA and lymphoma protocols have been used, with neither one demonstrating a clear advantage over the other [102]. One retrospective study of 49 patients showed that rituximab added to a regimen of conventional immunosuppressants resulted in higher rates of disease control and decreased adverse effects compared to conventional therapy alone [105]. In a smaller study from Roux-Villet et al., 88% of refractory MMP patients saw a complete response after 2 cycles of rituximab, although 2 patients did die from infections [110]. A recent systematic review included 112 MMP patients treated with rituximab and found that over 70% had complete resolution within 8.7 months. The recurrence rate was 35.7%, and the most common side effects recorded were leukocytopenia and urinary tract infections [111]. Although data from randomized controlled trials is needed before rituximab can be broadly recommended for MMP, it appears to have significant and rapid efficacy in patients who have failed conventional treatments [91, 93, 110, 112]. Rituximab may be even more useful in a subset of ocular predominant MMP known as ocular cicatricial pemphigoid. Several studies have shown its ability to treat refractory cases and prevent permanent complications such as blindness and scarring [37, 113–117]. Treatment of less common variations of MMP, such as tracheal/bronchial MMP or paraneoplastic MMP, may also benefit from the addition of rituximab [118, 119].

Epidermolysis Bullosa Acquisita

Large clinical studies on the efficacy of rituximab in epidermolysis bullosa acquisita (EBA) are scarce [89, 100, 120, 121]. There are several encouraging case reports which have shown its effectiveness in recalcitrant cases after patients have failed conventional therapies, resulting in clinical improvement and occasionally long-term remission [100, 120, 122–130]. A retrospective analysis of 10 patients who received the lymphoma protocol found rituximab to be associated with complete resolution in EBA [131]. The efficacy of the RA protocol has also been established in a randomized open-label study [29•]. Additionally, the combination of rituximab with either IVIg or protein A immunoadsorption may be a particularly effective option for difficult-to-treat EBA cases [89, 121, 124, 127, 132]. Randomized controlled trials covering a larger number of patients are required to determine optimal protocols and indications, but the current evidence warrants consideration of rituximab as a second-line therapy in EBA [67, 102, 133].

Dermatomyositis

There have been a number of small and/or retrospective studies establishing the efficacy of rituximab in treating the extracutaneous features of dermatomyositis (DM). Refractory myositis and myositis-associated lung disease specifically have been relatively well-studied [134–153]. However, research on the treatment of cutaneous disease has provided mixed results [135, 151, 154–156]. In an open-label pilot trial of seven patients treated with rituximab (100 or 375 mg/m^2 weekly for 4 weeks), five patients who had documented skin findings saw improvement [154]. However, no validated skin scoring system was used. A study by Chung et al. of eight patients with moderate-to-severe skin disease given the RA protocol of rituximab did incorporate an objective disease severity index. Although three patients achieved partial remission at 24 weeks, the changes in skin severity scoring were not statistically significant, and the authors concluded that rituximab has only a minor effect on dermatomyositis skin disease [135]. The rituximab in myositis (RIM) trial is the sole large randomized controlled trial addressing this topic to date. Seventy-six adult and 48 juvenile DM patients were included who had failed conventional therapies. A total of 83% of patients who received rituximab had improvement in muscle disease and reduction in steroid dosage needed [151]. Post-hoc analysis of the study also demonstrated a beneficial effect of rituximab in cutaneous disease, although assessment by non-dermatologists and lack of a validated scoring system make the results difficult to interpret [155]. Seeing as current evidence for the use of rituximab in the treatment of cutaneous dermatomyositis is limited, it is typically reserved for recalcitrant cases and those associated with specific manifestations such as pulmonary disease [157]. Interestingly, the myositis antibody profile of patients may affect their individual response to rituximab, although further research is needed to characterize this association [158–161].

ANCA-Associated Vasculitis

The efficacy of rituximab has been shown in both remission induction and maintenance of ANCA-associated vasculitis (AAV). Two randomized controlled trials, RAVE and RITUXVAS, established the non-inferiority of rituximab (375 mg/m^2 weekly for 1 month) to cyclophosphamide (2 mg/kg) in remission induction for patients with granulomatosis with polyangiitis (GPA) and microscopic polyangiitis

(MPA) [162•, 163, 164]. The FDA approved the drug (375 mg² IV, weekly for 4 weeks) for treatment of GPA and MPA in 2011 [165]. Notably, eosinophilic granulomatosis with polyangiitis (EGPA) patients were not included in these trials. However, multiple systematic reviews suggest that the drug can be helpful in inducing remission in such patients as well [166, 167]. Regarding maintenance therapy, the MAIN-RITSAN trial of 115 patients demonstrated the advantage of a rituximab regimen (500 mg on days 0, 14, and months 6, 12, and 18) over azathioprine in preventing relapse up to a follow-up of 60 months [168, 169]. Furthermore, a follow-up randomized controlled trial compared the former fixed-dose rituximab regimen to a tailored one based on ANCA and B-cell level measurements every three months, with low and statistically similar relapse rates being recorded in both groups [170]. The MAINRITSAN 3 study demonstrated that, after an 18-month cycle of rituximab, prolonging therapy for 18 additional months is effective in preventing relapse [171]. This again, however, did not include patients with EGPA. Notably, PR3-antibody-positive patients had higher rates of relapse, indicating that long-term rituximab treatment may be particularly beneficial in this subgroup [171]. Finally, another large, randomized trial showed that rituximab is superior to azathioprine for relapse prevention in AAV and resulted in fewer adverse events [172]. In summary, rituximab is an important therapeutic option for induction and/or maintenance in AAV patients.

Cutaneous Polyarteritis Nodosa

The evidence for the use of rituximab for cutaneous polyarteritis nodosa (cPAN) is limited and comprised solely of case studies. Sonomoto et al. documented a 47-year-old with cutaneous involvement who improved following rituximab therapy (3 doses of 375 mg/m²) [173]. Other cases utilized alternative regimens of rituximab and included several pediatric cPAN patients [174, 175]. Rituximab has also proven to be useful in the rare subset of viral-associated PAN patients with HBV or HCV [176, 177]. Additional studies following rituximab usage in PAN provided mixed results [173, 178–180], and the most recent papers have shown anti-CD20 therapy to be ineffective in several patients [181–184]. Thus,

Table 1 Evidence for rituximab usage in dermatological conditions

Disease	Recommendation
Pemphigus	- FDA approved first-line treatment for moderate-severe pemphigus-Over 85% of PV patients show complete resolution following RTX as adjuvant therapy with either LP or RP [4, 5, 9, 11, 12] - Effective in PF and childhood PV [6, 78–82]
Pemphigoid	- Third-line option reserved for refractory BP cases [84] - Effective third-line option for refractory MMP [67, 103] - May treat and prevent complications of recalcitrant OCP [37, 113–117]
Epidermolysis bullosa acquisita	- Second-line therapy [67, 102, 133] - Case reports show benefit in refractory cases [100, 120, 122–130] - Both LP and RP have been shown efficacy [29•, 131] - May be particularly useful for refractory cases when combined with IVIG or IA [89, 121, 124, 127, 132]
Dermatomyositis	- Typically reserved for recalcitrant cases and those associated with specific manifestations like pulmonary disease [157] - Mixed results for treatment of cutaneous disease [135, 154]
ANCA-associated vasculitis	- FDA approved for treatment of GPA and MPA [165] - RCTs utilizing both LP and RP show efficacy in induction and maintenance [162•, 163, 164, 168–172] - Systematic reviews show benefit in EGPA patients as well [166, 167]
Cutaneous polyarteritis nodosa	- Limited evidence and not recommended as primary choice in PAN - Studies have provided mixed results, with most recent showing ineffectiveness [173–175, 178–184] - May be useful in rare subsets of PAN associated with HBV/HCV [176, 177]
Cryoglobulinemia	- May be a useful and safe choice in treating cryoglobulinemic vasculitis, particularly in severe cases - Multiple RCTs have shown efficacy of both LP and RP [187–189, 190•] - Dramatic clinical improvements in refractory cases documented when combined with belimumab [191]
Cutaneous lupus erythematosus	- Limited and conflicting data - Observational studies of RP + IV methylprednisone or cyclophosphamide showed varying response rates [199–202] - Subgroup analysis suggests clinical benefit in ACLE, but no efficacy in SCLE or DLE

RTX rituximab, *PV* pemphigus vulgaris, *PF* pemphigus foliaceus, *LP* lymphoma protocol, *RP* RA protocol, *MMP* mucous membrane pemphigoid, *OCP* ocular cicatricial pemphigoid, *BP* bullous pemphigoid, *EBA* epidermolysis bullosa acquisita, *DM* dermatomyositis, *AAV* ANCA-associated vasculitis, *GPA* granulomatosis with polyangiitis, *MPA* microscopic polyangiitis, *EGPA* eosinophilic granulomatosis with polyangiitis, *CPN* cutaneous polyarteritis nodosa, *HBV* hepatitis B, *HCV* hepatitis C, *CLE* cutaneous lupus erythematosus, *ACLE* acute cutaneous lupus erythematosus, *SCLE* subacute cutaneous lupus erythematosus, *DLE* discoid lupus erythematosus, *IA* immunoadsorption

rituximab is currently not recommended as a primary choice in PAN. A 2019 case series out of Japan focused exclusively on cPAN. Thirty-six patients with cPAN were divided into groups based on the presence or absence of ulcers and neuritis. A total of 13% of the ulcer-type cPAN patients were treated with rituximab after failing more conventional therapies such as cyclophosphamide [185, 186].

Cryoglobulinemia

A systematic review from 2019 examined three randomized controlled trials which included 118 cryoglobulinemia patients [52, 187–189, 190•]. Damonacco et al. found that 375 mg/m^2 of weekly rituximab for 4 weeks added to a regimen of pegylated interferon alpha plus ribavirin resulted in higher rates of complete response than the same regimen without rituximab [187]. Divita et al. demonstrated significantly decreased disease activity in patients who received RA protocol rituximab, which remained stable up to 24 months [188]. Additionally, improved rates of remission were seen in rituximab-treated patients in a study from Sneller et al. [189]. Notably, a recent study showed that the combination of rituximab with the anti-BLyS monoclonal antibody belimumab resulted in dramatic clinical improvements in all four refractory cryoglobulinemic vasculitis patients included [191]. Several other cohort studies and case reports over the years have demonstrated the efficacy of rituximab in cryoglobulinemia [192–195]. When taken together, the current evidence suggests that rituximab may be a useful and safe choice in the treatment of cryoglobulinemic vasculitis, particularly in severe cases with neurological or renal involvement, or the presence of ulcers [3, 194]. However, the risk of adverse events such as rituximab-associated disease flares should be considered [196–198].

Cutaneous Lupus Erythematosus

There is limited and conflicting data regarding the efficacy of rituximab in treating cutaneous lupus erythematosus (CLE). A 2020 systematic review including over 7000 CLE patients identified just three observational studies in which rituximab was used [199–202]. Each of these studies utilized the RA protocol combined with either IV methylprednisone or cyclophosphamide. Results were mixed, with one study showing a poor response rate of 35% [201] while the others showed beneficial effects with response rates of 71–76% [200]. On subgroup analysis, rituximab provided improvement in acute cutaneous lupus erythematosus (ACLE) patients, while no efficacy was demonstrated in new-onset CLE, subacute cutaneous lupus erythematosus (SCLE), or discoid lupus erythematosus (DLE) patients. However, these conclusions are limited by relatively small sample sizes (< 50 patients) and the use of rituximab solely as an adjuvant

in combination with other medications. Additionally, limited case report data suggests that there may be a use for rituximab in lupus panniculitis [203].

A summary of the evidence for the use of rituximab in the various dermatologic conditions discussed above can be found in Table 1.

Conclusions

B-cell-directed therapies have revolutionized the treatment of PV. However, their utility in dermatology is not limited to this disease, which has an on-label indication. Rituximab can be helpful in other autoimmune blistering disorders, though the kinetics of response and relapse rates likely differ substantially between different diseases. In cutaneous lupus, polyarteritis nodosa, and the skin manifestations of dermatomyositis, its utility is less clear.

Compliance with Ethical Standards

Conflict of Interest KTA has served as a consultant for Astra Zeneca, Argenx, and Akari therapeutics. KTA has received research funding from Astra Zeneca and Kabafusion.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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