The safety of rituximab for the treatment of autoimmune blistering diseases: a systematic review

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BACKGROUND

The anti-CD20 antibody rituximab has been shown to improve response rates in patients with autoimmune blistering diseases. However, the safety profile of rituximab is unclear. We aimed to systematically evaluate reports of complications.

PURPOSE

Studies have demonstrated infusion reactions, infections, and laboratory abnormalities to generally be the leading adverse event of rituximab treatment regardless of disease, and we did not expect rituximab, when used for autoimmune blistering diseases, to exhibit a markedly different adverse event profile given similar dosing among indications. We were careful to highlight the non-infectious complications of rituximab treatment in our review that providers may not be as aware of.

METHODS

Searches were run in the following databases on April 16, 2019: MEDLINE (Ovid), PubMed, EMBASE (Elsevier), Cochrane Library (Wiley), World Health Organization's Global Index Medicus, CINAHL Complete (EBSCO), Scopus, and the Web of Science Core Collection. The following sources were searched between April 16, 2019 and May 02, 2019 to find grey literature not captured by Scopus and Web of Science: TRIP Database, ClinicalTrials.gov, International Standard Registered Clinical/soCial sTudy Number (ISRCTN) and the WHO International Clinical Trials Registry Platform. We also used the Canadian Agency for Drugs and Technologies in Health (CADTH) Grey Matters checklist (Mendeley supplemental Appendix 1) to identify other relevant grey literature sources and searched select conference proceedings and recent issues of relevant journals. Detailed search strategies can be found in Mendeley supplemental Appendix 2.

All data from clinical trials, case reports, case series, and spontaneous reporting schemes were included in this review. Only human studies assessing the use of rituximab in patients with pemphigus vulgaris, pemphigus vegetans, mucous membrane pemphigoid (cicatricial pemphigoid), bullous pemphigoid, linear IgA disease, and epidermolysis bullosa acquisita were included. The co-existence of comorbidities, such as malignancies, and other autoimmune diseases, significantly increases the risk of infection. To best control for this potential confounding variable and aim to isolate adverse events associated solely with rituximab, data from patients with other immunosuppressive conditions (such as organ transplant, HIV infection, active cancer, systemic lupus, ANCA associated vasculitis, and congenital immunodeficiency) were excluded (Figure 1).

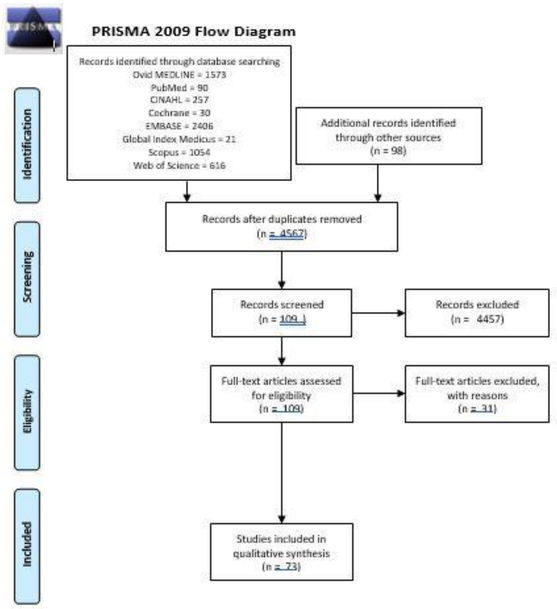

Figure 1. PRISMA Flowchart.

RESULTS

The literature search identified 4,567 articles. After screening titles and abstracts against the inclusion and exclusion criteria and assessing full texts, 84 articles were finally included in a narrative synthesis. 74 articles consisted of 6 clinical trials, 42 cohort studies, 12 case series, and 14 case reports, which included 1429 patients. There were 61 cases of bullous pemphigoid, 1126 cases of pemphigus vulgaris, 129 cases of cicatricial pemphigoid, 93 cases of pemphigus foliaceus, 2 cases of pemphigus vegetans, 14 cases of epidermolysis bullosa acquisita and 2 cases of IgA pemphigus. Characteristics of these articles including year, first author, sample size, design, levels of evidence according to the Oxford Centre for Evidence-based Medicine, underlying condition, adverse events, rituximab cycles/infusion/dosage/m^2, and comedication were recorded.

There were 300 patients with adverse events caused by rituximab. Out of the total patients, we classified 193 patients as having minor adverse events (13.6%) and 107 (8%) as having severe adverse events. We herein list totals of various adverse events, irrespective of patient number (for example, one patient may have had sepsis leading to death, and a herpes infection; this would count as 3 events). We tabulated a total of 213 incidents of major adverse events, with the majority infections and complications of infection such as sepsis and death. 4 of the 20 tabulated deaths were attributed by authors to non-infectious causes, including a patient with a history of cardiac disease who died 10 days after introduction of rituximab, an immobilized patient with history of cardiac disease who suffered a thromboembolic event, a patient who died following gastric perforation, and two causes which were unknown to authors In total, non-infectious complications represented 14.5% of major incidents and included 3 cases of cancer (prostate cancer, metastatic breast cancer, and mucoepidermoid carcinoma), 2 disease exacerbations, 7 infusion reactions requiring cessation of treatment such as severe angioedema, 2 cases of pulmonary embolism, 7 cases of deep vein thrombosis, and 1 case each of thromboembolism, cavernous sinus thrombosis, gastrointestinal bleed, gastric perforation, recurrent diarrhea, diarrhea with loss of consciousness and hospitalization, exudative enteropathy, Stevens-Johnson syndrome, and nephrotoxicity.

Patients with minor adverse events represented 13.6% of all patients tabulated, with totals of various minor adverse events, irrespective of patient as tabulated above. We tabulated 267 total incidents of minor adverse events. Infusion reactions were the most common minor adverse event, representing 143 cases. Infusion reactions necessitating hospitalization or discontinuation of treatment were classified as major adverse events. Most minor adverse events other than infusion reactions (32%) were infectious, detailed by organ system in Table 2. Noteworthy non-infectious minor adverse events constituted 23% of incidents and included 26 laboratory abnormalities such as anemia, liver enzyme elevations, granulocytopenia, leukopenia, neutropenia, hypogammaglobulinemia, hypergammaglobulinemia, elevated LDL, pancytopenia, and thrombocytopenia, 4 cases of altered mental status, and 1 case each of erythema nodosum, psoriasis flare, and lichen planus.

Adverse effect	Reported cases
Total Adverse Events	485
Major	213
Death	20
Infectious Total	123
Noninfectious Total	31
Pulmonary embolism	2
Gastric perforation	1
Recurrent diarrhea	1
Diarrhea with loss of consciousness and hospitalization	1
Exudative enteropathy	1
Gastrointestinal bleed	1
Stevens-Johnson Syndrome	1
Cardiac failure	1
Deep vein thrombosis	7
Thromboembolism	1
Cavernous sinus thrombosis	1
Nephrotoxicity	1
Disease exacerbations	2
Cancer	3
Infusion reaction requiring cessation	7
Minor	267
Infusion reaction	143
Infectious	47
Neither infusion reaction or infectious total	77
Laboratory abnormalities	26
Altered mental status	4
Psoriasis flare	1
Erythema nodosum	1
Lichen planus	1
Nonspecific gastrointestinal disorders	8

Table 1. Adverse Event Summary

Study	Sample Size	Design	LOE	Underlying Condition	Adverse event	Cycles received/infusions/ dosage/m² treatment	Comedication at time of rituximab
Study 1	7	Cohort	2	Bullous pemphigoid, cicatricial pemphigoid, pemphigus vulgaris	Death (infectious) sepsis, hypogammaglobulinemia, herpes zoster, pulmonary embolism, bacterial pneumonia, exudative enterocolitis, Clostridium enteropathy, parainfluenza pneumonia	1 cycle: 375 mg per week for 4 weeks	Dexamethasone, azathioprine, mycophenolate, cyclophosphamide, methylprednisolone, dapsone
Study 2	71	Cohort	2	Bullous pemphigoid, Pemphigus vulgaris, Pemphigus vegetans, paraneoplastic pemphigus*, pemphigus foliaceus, epidermolysis bullosa acquisita	Death (infectious) sepsis, pneumocystis infection, community acquired pneumonia, deep vein thrombosis, infectious arthritis	1-4 cycles, then monthly or every 2 weeks: 375 mg per week for 4 weeks	Methotrexate, cyclophosphamide, IVIG, mycophenolate, cyclosporine, steroids
Study 3	7	Cohort	2	Cicatricial pemphigoid, bullous pemphigoid	Death (non-infectious)	1-2 cycles: 375 mg per week for four weeks	Immunosuppressants and corticosteroids given but not specified
Study 4	36	Cohort	2	Pemphigus vulgaris, pemphigus foliaceus	Sepsis, infusion reactions, herpes simplex virus, anemia, deep vein thrombosis, infusion reaction requiring cessation, disseminated herpes infection, granulocytopenia	1-2 cycles: 375 mg per week for four weeks	Prednisolone, methylprednisolone, azathioprine, mycophenolate, methotrexate, immunoadsorption
Study 5	47	Cohort	2	Pemphigus vulgaris	Infusion reactions, nonspecific tinea infections, herpes zoster, infusion requiring cessation	1-3 cycles: 1000 mg twice 2 weeks apart	Prednisone, mycophenolate mofetil, azathioprine
Study 6	10	Cohort	2	Pemphigus vulgaris	Death (infectious) sepsis, infusion reaction, angioedema, infusion requiring cessation	1 cycle: 1000 mg twice 2 weeks apart in adults, 375 mg twice 2 weeks apart in children	Mycophenolate mofetil, prednisolone
Study 7	45	Clinical Trial	1	Pemphigus vulgaris	Pneumonia, infusion reaction, deep vein thrombosis, Stevens-Johnson syndrome, skin abscess, cavernous sinus thrombosis, lungabscess, disseminated herpes infection	1-3 cycles: 375 mg per week for 4 weeks	prednisolone
Study 8	100	Cohort	2	Pemphigus vulgaris, pemphigus foliaceus	Infusion reactions, infusion requiring cessation, bilateral paronychia, lichen planus	1-4 cycles: 1000 mg twice 2 weeks apart, followed by 500 mg IV if clinically warranted at 6-month intervals or repeated full dosing	Received, agents not specified
Study 9	26	Cohort	2	Pemphigus vulgaris	Death (non-infectious) infusion reactions, thromboembolism	1-4 cycles: 1000 mg twice 2 weeks apart, 375 mg once a week for 4 weeks	Corticosteroids, azathioprine, mycophenolate
Study 10	25	Cohort	2	Pemphigus vulgaris	Disease exacerbation, cellulitis, pneumonia,	1-3 cycles: 1000 mg 2 weeks apart, 640 mg 2 weeks apart	Prednisolone,azathioprine
Study 11	24	Cohort	2	Cicatricial pemphigoid	Pneumonia,leukopenia, anemia, nephrotoxicity, pancytopenia, gastrointestinal bleed, infusion reaction requiring cessation	1-3 cycles: 1000 mg twice 2 weeks apart	Prednisone, mycophenolate, dapsone, azathioprine, IVIG, cyclophosphamide, cyclosporine, etanercept, methotrexate
Study 12	32	Cohort	2	Cicatricial pemphigoid	Leukopenia, Epstein-Barr virus, anemia, liver enzyme elevation, sinus infection	1 cycle: 375 mg per week for 8 weeks, then monthly for 4 months	IVIG, dapsone, cyclosporine, cyclophosphamide, methotrexate, mycophenolate
Study 13	45	Cohort	2	Pemphigus vulgaris, pemphigus foliaceus	Death (non-infectious) acute respiratory distress syndrome, gastric perforation	1-4 cycles: 375 mg weekly for 2 weeks	Prednisone, azathioprine, mycophenolate, cyclosporin, dapsone, cyclophosphamide, IVIG, methylprednisolone
Study 14	114	Cohort	2	Pemphigus vulgaris	Infusion reactions, nonspecific tinea infection, herpes zoster, pulmonaryembolism, tuberculosis,pleural effusion, recurrent diarrhea, bacterial pneumonia	1-2 cycles: 375 mg once a week for 4 weeks, 1000 mg twice 2 weeks apart, 3 doses of 500 mg each 1 week apart followed by 500 mg 3 months later	Cyclophosphamide, mycophenolate, azathioprine, methotrexate, dexamethasone, prednisolone
Study 15	46	Clinical Trial	1	Pemphigus vulgaris	Sepsis, pneumonia, liver enzyme elevation, deep vein thrombosis, spondylodiscitis, cardiac failure, depression, femur fracture, vertebrafracture, wrist fracture, rotator cuff rupture, myopathy, Cushing syndrome, major skin atrophy.	1000 mg of intravenous rituximab on days 0 and 14, and 500 mg at months 12 and 18	prednisone
Study 16	6	Case Series	4	Pemphigus vulgaris, Pemphigus foliaceus	Infusion reaction, liver enzyme elevation	...	Corticosteroids and immunosuppressants used but agent not specified
Study 17	20	Clinical Trial	1	Pemphigusvulgaris	Infusion reactions, erythema nodosum, onychomycosis, herpes labialis, tuberculosis	1-3 cycles: 1000 mg twice 2 weeks apart	Immunosuppressants and corticosteroids used but agents not specified
Study 18	9	Cohort	2	Pemphigus vulgaris	Upper respiratory infection, nonspecific infections, herpes simplex virus, oral candidiasis, tinea pedis, lymphopenia, cytomegalovirus, balanitis trochanteric bursitis, herpes supraglottitis,	1-3 cycles: 500 mg twice with 2 week interval	Prednisolone, mycophenolate, azathioprine
Study 19	28	Cohort	2	Bullous pemphigoid, cicatricial pemphigoid, epidermolysis bullosa acquisita	Death (infectious and unknown causes) sepsis, pneumocystis infection,urinary tract infection, upper respiratory infection, hospitalizations, altered mental status, infusion reaction, herpes simplex virus, herpes labialis, psoriasis flare, diarrhea, erysipelas, infusion reactions requiring cessation	1-2 cycles: 1000 mg twice with 2 week interval, 500 mg twice with 2 week interval	Prednisolone, cyclophosphamide, dapsone
Study 20	20	Clinical Trial	1	Pemphigus vulgaris	Cancer, hospitalizations (nonspecific), altered mental status	1-3 cycles: 1000 mg twice 2 weeksapart, 375 mg per week for 4 weeks	Prednisone, mycophenolate, azathioprine, dapsone, doxycycline, methotrexate
Study 21	10	Clinical Trial	1	Bullous pemphigoid, pemphigus foliaceus, pemphigus vulgaris	Sepsis, pneumocystis infection,infections (nonspecific), hypogammaglobulinemia, furuncle, dental caries, hypergammaglobulinemia, elevated low density lipoprotein, gastrointestinal (nonspecific)	1 cycle, 375 mg per week for 4 weeks	Azathioprine, mycophenolate, corticosteroids, cyclosporin
Study 22	23	Cohort	2	Pemphigus vulgaris	Eczema herpeticum, infusion reaction, cytopenia,cellulitis, molluscum	1-2 cycles: 375 mg per week for four weeks, two doses of 1 g each two weeks apart, 375 mg per week for 3 weeks	IVIG
Study 23	1	Case report	4	Bullous pemphigoid	neutropenia	2 cycles: 375 mg per week for four weeks	...

Table 2. Selected Studies involving non-infectious adverse events

DISCUSSION

Infections are among the leading causes of death in pemphigus vulgaris and bullous pemphigoid patients. While rituximab has become a first-line therapy for immunobullous disease and is now FDA-approved to treat pemphigus, we feel it is important for practitioners to note the range of potential side effects that have been reported in its use. Our study of rituximab in immunobullous disease was able to find causes of death largely due to sequelae from infection, such as sepsis leading to multi-organ failure and ARDS, but with a few from distinct etiologies such as thromboembolism and gastric perforation. Furthermore, in the midst of successful treatment of the various autoimmune bullous diseases, a range of adverse events across multiple organ systems were commonly reported, with major non-infectious complications primarily cardiovascular, gastrointestinal, renal, cutaneous, and neoplastic in origin, with no reports of non-infectious pulmonary, or neurologic complications that have been reported with general rituximab usage. Minor complications featured primarily infusion reactions, with a significant proportion represented by laboratory abnormalities such as hypogammaglobulinemia or neutropenia. While an incidence rate cannot be calculated from this study, the results of reviewing the literature suggest some sort of adverse event is not uncommon during rituximab usage.

Limitations of the study included relatively few studies available for inclusion after application of exclusion criteria given the relative novelty of rituximab use for blistering diseases. Methods of reporting adverse events were also different between articles; some did not specify what type of infection was occurring, while others only focused on major adverse events and did not report on what would be considered minor adverse events based on our set criteria. Additionally, at times studies did not list information on adjuvant immunosuppressants used that may have been interesting to evaluate. Finally, because autoimmune blistering diseases are likely to have been followed by dermatologists, cutaneous side effects are more likely to have been reported.

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