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

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Contributors' Statements

Mr. Mohammed assisted with the search, excluded studies, assessed data, conceptualized the report, and reviewed and revised the manuscript.

Dr. Hekman conceptualized the report, assessed data, and reviewed and revised the manuscript.

Dr. Li assessed search data and excluded studies.

Ms. Misquith performed the search and conceptualized the search strategy.

Dr. Rahnama-Moghadam conceptualized the report and reviewed and revised the manuscript.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Autoimmune bullous diseases consist of various diseases where autoantibodies are produced against cellular adhesion proteins and components of the basement membrane of the skin and mucous membranes. The anti-CD20 monoclonal antibody rituximab is considered the first-line treatment in new-onset moderate-to-severe pemphigus and/or patients who do not achieve clinical remission with systemic corticosteroids or immunosuppressive agents[1]. 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[2] . We were thus careful to highlight the non-infectious complications of rituximab treatment that providers may not be as aware of.

A comprehensive literature search of academic research databases was undertaken between April 16, 2019 and May 02, 2019; grey literature sources were included to minimize publication bias (Mendeley supplemental Appendix 1). Detailed search strategies can be found in Mendeley supplemental Appendix 2. Using the Common Terminology Criteria for Adverse Events (CTCAE) v5.0, we classified Grade 1 or 2 events as minor and Grade 3, 4, or 5 events as major[3].

73 articles met our eligibility criteria and were reported with PRISMA (Mendeley supplemental Figure 1). Characteristics of articles featuring non-infectious events 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 (I) (data for all articles is available in Mendeley supplemental Table I; citations of included studies removed due to journal citation constraints and are available from the authors upon request)

300 of 1438 patients extracted had adverse events caused by rituximab. 107 (8%) had major adverse events, and 193 patients (13.6%) had minor adverse events. Non-infectious complications represented 14.5% of major incidents, and 23% of minor incidents were neither infectious nor infusion reactions. We herein list totals of each non-infectious incident (II) (All incident counts available in Mendeley supplemental Table II).

Our study of rituximab in immunobullous disease found causes of death largely due to sequelae from infection, such as sepsis leading to multi-organ failure, but few were from distinct etiologies such as thromboembolism and gastric perforation. Severe non-infectious complications represented a range of organ systems including cardiovascular, pulmonary, gastrointestinal, cutaneous, and renal. Minor complications featured mostly infusion reactions, with a significant proportion represented by laboratory abnormalities.

Limitations of the study included relatively few studies available for inclusion given rituximab's novelty. Differing adverse event reporting methodology among articles complicated classification and discernment of causality due to corticosteroids and/or immunosuppressives.

Finally, because blistering diseases are followed by dermatologists, cutaneous side effects are more likely to have been reported.

While rituximab has become a first-line therapy for immunobullous disease, we feel it is important for practitioners to note the range of potential side effects. Because this study included multiple different study designs along with studies without a comparator group, its data should be a starting point for future studies.

References

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Table I. Reported studies involving non-infectious adverse events

Study	Sample Size	Design	LOE	Underlying Condition	Adverse event	Cycles received/infusions/ dosage/m^2	Comedication at time of rituximab treatment
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, lung abscess, 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, pulmonary embolism, 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, vertebra fracture, 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	Pemphigus vulgaris	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 weeks apart, 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	…

*diseases excluded from our analysis

Table II: Noninfectious Adverse Event Summary

Adverse effect	Reported cases
Total Adverse Events	485
Major	213
Death Total	20
Death Infectious Cause	16
Death Noninfectious Cause	4
Infectious Total	123
Noninfectious Total	31
Pulmonary embolism	2
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Gastrointestinal bleed	1
Stevens-Johnson Syndrome	1
Cardiac failure	1
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Thromboembolism	1
Cavernous sinus thrombosis	1
Nephrotoxicity	1
Disease exacerbations	2
Cancer	3
Infusion reaction requiring cessation	7
Minor	267
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Infectious	47
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Laboratory abnormalities	26
Altered mental status	4
Psoriasis flare	1
Erythema nodosum	1
Lichen planus	1
Nonspecific gastrointestinal disorders	8

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