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SHORT REPORT

Off-label use of rituximab for dermatologic conditions: A single center review

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Abstract

Background: Rituximab (RTX) has been utilised off-label for a variety of dermatological indications beyond pemphigus vulgaris. Efficacy has been reported in other immunobullous disorders, inflammatory dermatoses and connective tissue diseases.

Objectives: To assess the off-label use of RTX in our centre with respect to indications, frequency and duration of treatment, efficacy, and adverse events.

Methods: Charts were retrospectively reviewed for all patients who received dermatologist-prescribed RTX infusions off-label at our centre between 2009 and 2022. Efficacy was categorised based on reported percentage reduction of disease activity: very good (75%–100%), good (50%–74%), partial (25%–49%) and none (0%–24%).

Results: Twenty-nine patients received RTX off-label during this time period. Infusions were discontinued in 28% ($n = 8$), due to insufficient clinical response. Median treatment duration for those on 6-12-monthly regular infusions was 2.4 years (range 0.5–11 years). Indications included cutaneous lupus ($n = 9$), mucous membrane pemphigoid ($n = 5$), pyoderma gangrenosum ($n = 6$), lichen planus ($n = 2$), dermatomyositis ($n = 1$), livedoid vasculitis ($n = 1$), sarcoidosis ($n = 1$), bullous pemphigoid ($n = 1$), pemphigus vulgaris, foliaceus and vegetans ($n = 1$ each). Clinical improvement was documented in 79% ($n = 23$); very good in 48% ($n = 14$), good in 17% ($n = 5$), and moderate in 14% ($n = 4$). Clinical efficacy in immunobullous disorders was 100% (9/9), 67% in cutaneous lupus (6/9), 33% in pyoderma gangrenosum (2/6), and 50% in lichen planus (1/2). No side effects were documented for 79% ($n = 23$). Adverse peri-infusion events were seen in three patients (10%). Four patients died during follow up; one due to neutropenic sepsis with a background of advanced malignancy, and three due to Covid-19.

Conclusions: RTX was prescribed for multiple off-label dermatological indications, often for recalcitrant disease. Responses were good overall, with

a reassuring safety profile. Three patients died of Covid-19; knowledge of the impact of RTX on the immune response and efficacy of vaccines is expanding and will continue to inform guidelines for RTX use in the post-Covid era.

KEYWORDS
dermatomyositis, lupus, pemphigoid, pemphigus, rituximab, therapeutics, vasculitis

BACKGROUND

Rituximab (RTX) is an anti-CD20 monoclonal antibody licensed to treat pemphigus vulgaris,[1] with growing evidence for off-label use for other dermatological indications, including immunobullous disorders and dermatomyositis.[2]

OBJECTIVES

This study aimed to explore the use of RTX in our department for off-label indications.

METHODS

Ethical approval was granted by the Clinical Research Ethics committee of the Cork Teaching Hospitals. All off-label prescriptions of RTX for dermatologic indications between 2009 and 2022 were retrospectively reviewed. Indications, frequency and duration of treatment, clinical response, and details of adverse effects were evaluated. To standardise clinical assessment across different conditions, a categorical assessment tool was used. Response was defined as very good (75%–100%), good (50%–74%), partial (25%–49%) and none (0%–24%).

RESULTS

Twenty-nine patients received RTX for off-label dermatologic indications during this period. Median age was 51 years (range 25–79 years), 66% ($n = 19$) were female. Indications for treatment included cutaneous lupus (31%, $n = 9$), pyoderma gangrenosum (21%, $n = 6$), mucous membrane pemphigoid (17%, $n = 5$), lichen planus (7%, $n = 2$), pemphigus foliaceus (7%, $n = 2$), pemphigus vegetans, dermatomyositis, livedoid vasculitis, sarcoidosis, and bullous pemphigoid ($n = 1$ each). Twenty patients (69%) had previously been treated with two or more immunosuppressant agents without satisfactory response (Table 1).

TABLE 1 Details of previous treatments of each patient, according to clinical diagnosis

Number	Diagnosis	Previous treatments
1	Bullous pemphigoid	PRED
2	Mucous membrane pemphigoid	PRED, AZA, MMF
3	Mucous membrane pemphigoid	PRED, IVMP, MMF
4	Mucous membrane pemphigoid	IVMP, MMF
5	Mucous membrane pemphigoid	PRED, MTX
6	Mucous membrane pemphigoid	PRED, IVIG, AZA, CYP
7	Pemphigus foliaceus	PRED, IVMP
8	Pemphigus foliaceus	PRED
9	Pemphigus vegetans	PRED
10	Cutaneous lupus – SCLE, SLE	IVMP, MTX
11	Cutaneous lupus – SCLE and MCTD	PRED
12	Cutaneous lupus – DLE	PRED, MTX
13	Cutaneous lupus – SCLE	MMF
14	Cutaneous lupus – DLE	MMF, CSA, IVIG, AZA, IFX
15	Cutaneous lupus – SCLE, SLE	PRED, MTX
16	Cutaneous lupus – DLE	MTX, IVIG
17	Cutaneous lupus – SCLE	PRED, MTX
18	Cutaneous lupus – SCLE	PRED, MTX, MMF
19	Dermatomyositis	PRED, IVMP, MTX
20	Sarcoidosis	PRED, IVMP, MTX, IFX
21	Lichen planus	Nil
22	Lichen planus	PRED, MMF
23	Livedoid vasculitis	PRED, MMF

TABLE 1 (Continued)

Number	Diagnosis	Previous treatments
24	Pyoderma gangrenosum	PRED, IFX, IVIG, CYP, USTE
25	Pyoderma gangrenosum	PRED
26	Pyoderma gangrenosum	PRED, CSA, MMF
27	Pyoderma gangrenosum	PRED, IFX
28	Pyoderma gangrenosum	PRED
29	Pyoderma gangrenosum	PRED, MMF

Abbreviations: AZA, azathioprine; CSA, ciclosporin; CYP, cyclophosphamide; DLE, Discoid lupus erythematosus; IFX, infliximab; IVIG, intravenous immunoglobulin; IVMP, intravenous methylprednisolone; MCTD, mixed connective tissue disease; MMF, mycophenolate mofetil; MTX, methotrexate; PRED, prednisolone; SCLE, subacute cutaneous lupus erythematosus; SLE, systemic lupus erythematosus; USTE, Ustekinumab.

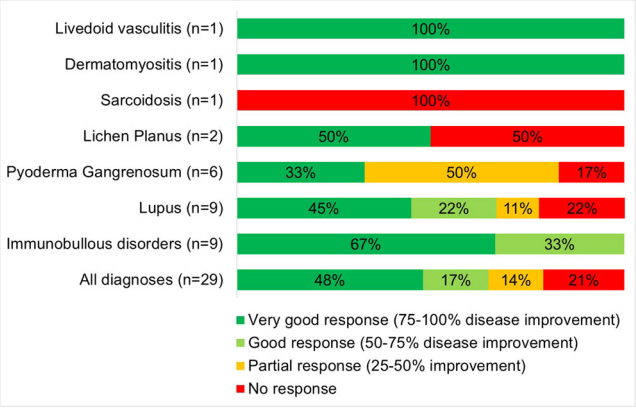

FIGURE 1 Response rates to rituximab according to diagnosis. Immunobullous conditions included mucous membrane pemphigoid, bullous pemphigoid, pemphigus foliaceus and pemphigus vegetans.

Clinical response (defined as 25%–100% improvement) was documented in 79% ($n = 23$). Response was very good (75%–100% reduction in disease activity or disease remission) in 48% ($n = 14$), good (50%–74% reduction) in 17% ($n = 5$), and partial (25-49% improvement) in 14% ($n = 4$) (Figure 1). No response was seen in 21% ($n = 6$).

Treatment was discontinued due to insufficient initial response in 27.5% of patients ($n = 8$). This lack of initial response prompting discontinuation was observed for pyoderma gangrenosum (three of six patients), discoid lupus erythematosus (two of three patients), lichen planus (one of two patients), sarcoidosis (one of one patients) and dermatomyositis (one of one patients). For those on regular infusions ($n = 21$), frequency was 6-monthly for 71% ($n = 15$), 3–4-monthly for 14% ($n = 3$) and 12-monthly for 14% ($n = 3$). Eleven patients (37%) were maintained on regularly scheduled infusions at the time of review. Disease remission in 24% ($n = 7$) allowed for discontinuation of infusions. Treatment was discontinued due to Covid-19 infection in two patients, who subsequently died. One patient was lost to dermatology follow up.

Treatment-related adverse events were reported in 21% of patients ($n = 6$). Three patients (10%) had infusion-related adverse effects, which were mild and transient (fatigue, pruritus, paraesthesia, and mild urticaria). Two patients had recurrent respiratory infections, but also had concurrent contributory comorbidities. Four patients died during the period (median age 72 years). One patient died due to neutropenic sepsis with a background of advanced malignancy, before the Covid-19 pandemic. Three patients died of Covid-19, with a median time of 10.1 months (range 0.5–26 months) from most recent infusion, and 19.6 months (range 17–27 months) from commencement of RTX. Two patients who died of Covid-19 had stopped RTX infusions before the pandemic. One patient who continued RTX infusions throughout the pandemic and died of Covid-19 had multiple cardiovascular and metabolic comorbidities. Two patients who died of Covid-19 were vaccinated and one died before vaccines were available.

CONCLUSIONS

In this study, RTX was used for multiple off-label dermatologic indications. Most patients had been on multiple immunomodulatory treatments. Clinical efficacy was greatest in pemphigus and pemphigoid. Though variable in other indications, only 21% of patients had no clinical response. Most patients treated with RTX for cutaneous lupus had significant benefit, though response varied, in keeping with previous studies.[3] Efficacy in pyoderma gangrenosum (PG) has rarely been reported, and only two of six patients with recalcitrant disease had disease improvement.[4,5] While the role of B cells in PG has not been fully elucidated, PG is associated with several haematologic conditions with aberrant B-cell populations.[6] However, RTX has also been associated with several cases of paradoxical drug-induced PG.[6] Disease remission was achieved in one patient with lichen planus. RTX was chosen in this case for severe erosive oral and genital disease that was recalcitrant to other treatments. However, the underlying mechanism for its efficacy in lichen planus,

which is predominantly T-cell mediated, has yet to be fully elucidated.[7]

Treatment was well tolerated overall. Three patients died due to Covid-19, though only one had been actively treated with RTX during the pandemic. There are concerns about insufficient Covid-19 vaccine responses with RTX due to B-lymphocyte depletion.[8] Recent research has shown that, in patients with pemphigus vulgaris treated with RTX, the SARS-CoV-2 vaccine–elicited specific T-cell–mediated immunologic memory is largely intact, but there is an extremely low humoral antibody response, which is considered the most representative of vaccine efficacy.[9] Optimal time between RTX exposure and Covid-19 vaccination has been suggested to be 9 months.[10] International guidelines for RTX use in pemphigus vulgaris[11,12] do not yet reflect Covid-19 vaccination scheduling advice.

In conclusion, this real-world review found that RTX was prescribed for multiple off-label dermatological indications, often for recalcitrant disease. Responses were excellent overall, with a reassuring safety profile, although three patients with multiple comorbidities died of Covid-19. Knowledge regarding the impact of RTX exposure on vaccine response continues to expand, and will guide future management of our RTX-treated patients.

AUTHOR CONTRIBUTIONS

Cathal O'Connor, John F. Bourke and Michelle Murphy conceived of the research idea. Cathal O'Connor, John F. Bourke, Michelle Murphy, Emma Porter, Paula Finnegan and Amy Long created the patient database. Emma Porter, Paula Finnegan and Amy Long collected data on patients. Emma Porter and Cathal O'Connor wrote the first draft. Cathal O'Connor, John F. Bourke, Michelle Murphy, Emma Porter, Paula Finnegan and Amy Long reviewed the initial draft. Emma Porter and Cathal O'Connor subsequently redrafted the manuscript and submitted it for publication.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Available on request. The data underlying this article will be shared on reasonable request to the corresponding author.

ETHICS STATEMENT

Ethical approval was granted by the Clinical Research Ethics committee of the Cork Teaching Hospitals.

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