Medicines Adverse Reactions Committee

Meeting date	12/09/2024	Agenda item	3.2.3
Title	**Anti-CD20 antibodies and pyoderma gangrenosum**		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice
Active ingredient Obinutuzumab Ocrelizumab Ofatumumab Rituximab	**Product name** See Table 1	**Sponsor**	
PHARMAC funding	See Table 1 for details		
Previous MARC meetings	This topic has not been previously reviewed by the MARC		
International action	Switzerland: prescribing information updated for the class USA: prescribing information updated for rituximab and ocrelizumab		
Prescriber Update	None		
Classification	Prescription medicine		
Usage data	See section 2.2.2		

Advice sought	**The Committee is asked to advise:**
	• Whether there is evidence for an association between pyoderma gangrenosum and anti-CD20 antibodies as a class (obinutuzumab, ocrelizumab, ofatumumab, rituximab)?
	  ○ If yes, are data sheet updates required?
	• If there is no evidence for the class, is there evidence for an association between pyoderma gangrenosum and one or more anti-CD20 antibodies, and if so, which one(s)?
	  ○ Are data sheet updates required for the specified anti-CD20 antibodies?
	• Does the topic require further communication, other than MARC's remarks in Prescriber Update?		

Table of Contents

1 PURPOSE 3
2 BACKGROUND 3
2.1 Pyoderma gangrenosum 3
2.1.1 Drug-induced PG 5
2.2 Anti-CD20 antibodies 6
2.2.1 Approved products 6
2.2.2 Usage data 8
2.2.3 Indications, dosing and mechanism of action 8
2.3 Prescribing information – pyoderma gangrenosum 10
2.3.1 New Zealand 10
2.3.2 International 11
3 SCIENTIFIC INFORMATION 13
3.1 Published literature 13
3.1.1 Drug-induced PG 13
3.1.2 Treating PG 32
3.2 Spontaneous reports 34
3.2.1 New Zealand 35
3.2.2 International (Vigilyze) 38
3.3 Company reports 41
[redacted] 41
[redacted] 41
4 DISCUSSION AND CONCLUSIONS 43
5 ADVICE SOUGHT 43
6 ANNEXES 43
7 REFERENCES 44

1 PURPOSE

In 2023, sponsors notified Medsafe about requests from the US Food and Drug Administration (FDA), the Swiss regulatory authority, Swissmedic, and the European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC) to update product information for anti-CD20 antibodies to include pyoderma gangrenosum (PG). Approved anti-CD20 antibodies in New Zealand are obinutuzumab, ocrelizumab, ofatumumab and rituximab.

The FDA requested PG be added as a postmarket adverse event of the US prescribing information for ocrelizumab. Swissmedic requested PG be added to the Swiss prescribing information for all anti-CD20 antibodies as a class. The PRAC requested the sponsors of rituximab-containing products to review the risk of PG.

The sponsors stated there were no plans to update the NZ prescribing information.

The purpose of this memo is to review the information on PG and the potential association with anti-CD20 antibodies.

2 BACKGROUND

2.1 Pyoderma gangrenosum

Pyoderma gangrenosum (PG) presents as a rapidly enlarging, very painful ulcer [1]. It is a reactive non-infectious inflammatory dermatosis falling under the spectrum of the neutrophilic dermatoses, which also includes Sweet's syndrome and Bechet's syndrome [2].

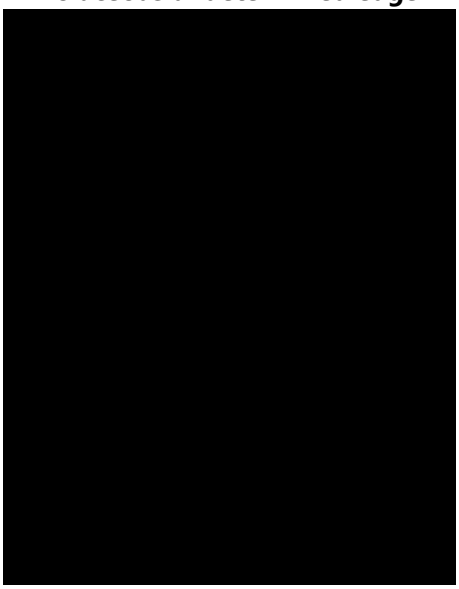
Despite its name, PG is neither an infectious nor gangrenous condition [1]. Neutrophils play a key role in the pathogenesis of PG and accumulate in the dermis. The immune dysregulation in PG has not yet been fully understood, but it involves T cells, neutrophils, and inflammatory mediators. Proinflammatory cytokines such as tumour necrosis factor alpha (TNFα), interleukin-1 (IL-1), IL-6, IL-8, IL-17, and IL-23 are upregulated in the skin with PG [3]. There may be a genetic predisposition [1].

PG is a rare disease, with an incidence of approximately 3 to 10 cases per million people per year [4]. It can affect individuals of any age, but is more common in those aged over 50 years [1]. The sex incidence ranges from being equal, to females being predominantly affected in up to 76% of cases [2].

Up to 50% of cases have underlying systemic conditions, with inflammatory bowel disease, rheumatological disorders and haematological malignancies the most frequently associated conditions [2]. PG may also be idiopathic or present in the setting of other autoinflammatory syndromes, such as PAPA (Pyogenic Arthritis, PG and Acne), PASH (PG, Acne, and Suppurative Hidradenitis), PAPASH (Pyogenic Arthritis, PG, Acne, and Suppurative Hidradenitis), and in a small proportion of SAPHO (Synovitis, Acne, Pustulosis, Hyperostosis, and Osteitis) cases [5].

There are several subtypes, with classic ulcerative as the most common form in approximately 85% of cases. This presents as an extremely painful erythematous lesion which rapidly progresses to a blistered or necrotic ulcer (Figure 1). There is often a ragged undermined edge with a violaceous/erythematous border. The lesion may be precipitated by minor trauma, a phenomenon known as 'pathergy'. The lower legs are most frequently affected, although PG can present at anywhere on the body. Other subtypes include bullous, vegetative, pustular, peristomal and superficial granulomatous variants [2].

Figure 1: Classical (ulcerative) pyoderma gangrenosum – a rapidly progressive painful ulcer with a violaceous undetermined edge



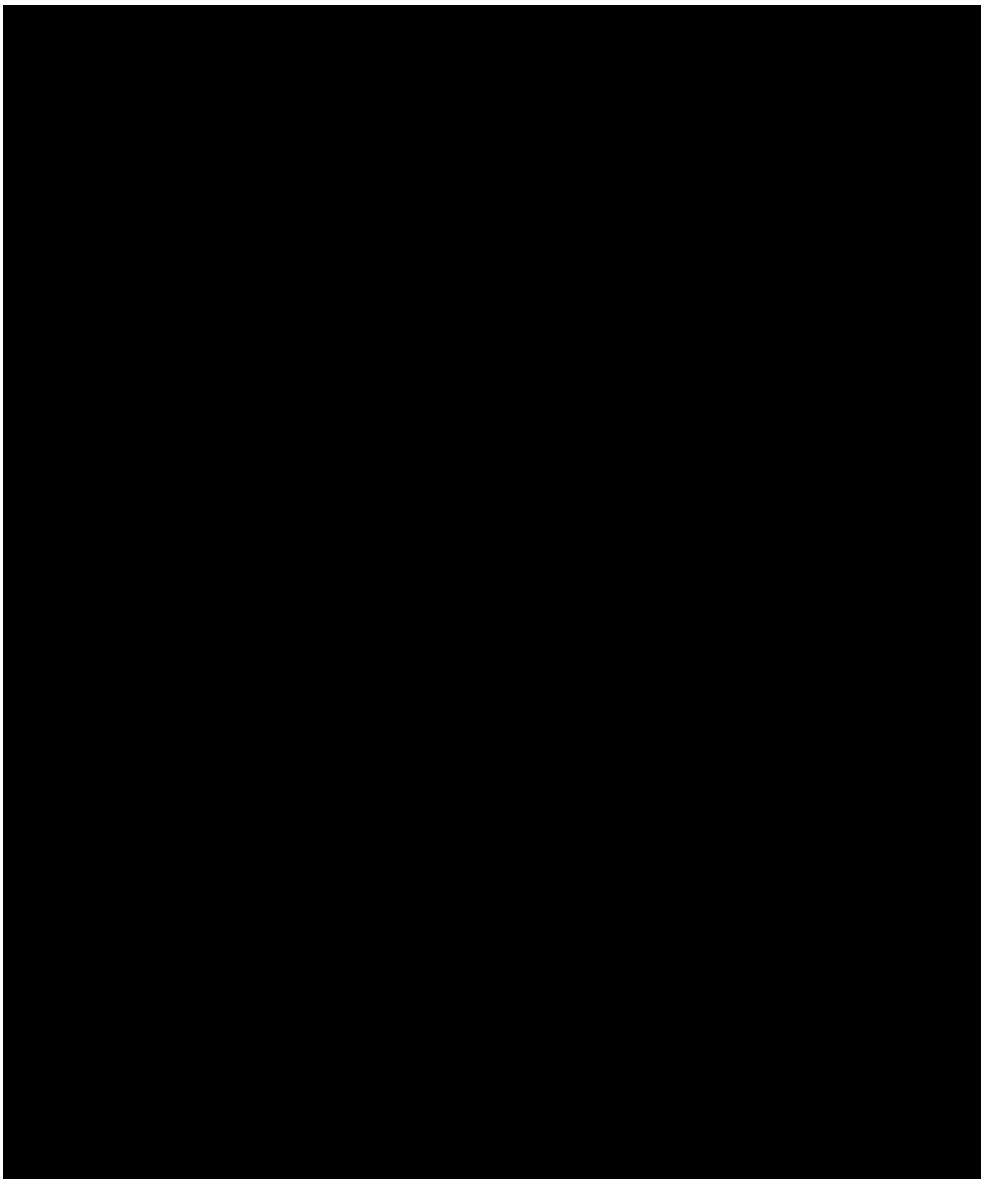
Source: George G, Deroide F and Rustin M. 2019. Pyoderma gangrenosum – a guide to diagnosis and management. *Clinical Medicine* (London, England) 19(3): 224-8. DOI: 10.7861/clinmedicine.19-3-224 (accessed 5 August 2024).

Injury to the skin is a common trigger, and a surgical trigger is well known and often misinterpreted as a wound infection [1]. Medicines, such as propylthiouracil, tyrosine kinase inhibitors, isotretinoin, TNFα inhibitors and granulocyte-colony stimulating factor, have also been implicated but the underlying disease for which the medicine was prescribed may be the triggering factor [1, 2].

Diagnosis of PG is challenging due to its variable presentation, clinical overlap with other conditions, association with several systemic diseases, and absence of defining histopathologic or laboratory findings [4]. The skin manifestations can be mistaken for a variety of infectious and non-infectious aetiologies, including cutaneous tuberculosis, leishmaniasis, sporotrichosis or other fungal infections, vasculitis, malignancy, thrombophilias, cellulitis, abscess, diabetic foot ulcer and other infectious diseases [6, 7]. Misdiagnosis may lead to inappropriate treatment with antibiotics with no benefit, and/or unnecessary surgical incision and debridement, which further exacerbates the lesion, ultimately leading to longer treatment periods and higher medical costs [6, 7].

Maverakis et al proposed a set of diagnostic criteria based on clinical history, presentation, histopathology and resolution pattern (Figure 2). There is 1 major criterion (biopsy of ulcer edge demonstrating neutrophilic infiltrate) and 8 minor criteria (exclusion of infection; pathergy; history of inflammatory bowel disease or inflammatory arthritis; history of papule, pustule, or vesicle ulcerating within 4 days of appearing; peripheral erythema, undermining border, and tenderness at ulceration site; multiple ulcerations, at least 1 on an anterior lower leg; cribriform or "wrinkled paper" scar(s) at healed ulcer sites; decreased ulcer size within 1 month of initiating immunosuppressive medication(s)). The presence of the major criterion plus 4 or more of the minor criteria yields a sensitivity of 86% and a specificity of 90% for pyoderma gangrenosum [4].

Figure 2: Diagnostic criteria for classic ulcerative pyoderma gangrenosum



Source: Maverakis E, Ma C, Shinkai K, et al. 2018. Diagnostic criteria of ulcerative pyoderma gangrenosum: A Delphi consensus of international experts (abstract only). *JAMA Dermatology* 154(4): 461-66. DOI: 10.1001/jamadermatol.2017.5980 (accessed 5 August 2024).

The management of PG relies mainly upon immunosuppression with no acknowledged treatment guidelines, but systemic corticosteroids and oral cyclosporine are frequently used medicines [3]. Treatment is usually successful in arresting the process, but complete healing may take months [1].

2.1.1 Drug-induced PG

Wu et al proposed several mechanisms for drug-induced PG, such as dysfunctional neutrophil migration and function, dysregulated inflammatory response, promotion of keratinocyte apoptosis and alteration of epigenetic mechanisms [8]. They identified 43 reports of drug-induced PG in the literature, including one for rituximab (Dixit et al, described in section 3.1.1.8), and Figure 3 shows their proposed pathogenic mechanism for each drug.

Figure 3: Proposed pathogenic mechanisms for drug-induced PG

Source: Wu B, Patel E and Ortega-Loayza A. 2017. Drug-induced pyoderma gangrenosum: a model to understand the pathogenesis of pyoderma gangrenosum. British Journal of Dermatology 177(1): 72-83. DOI: 10.1111/bjd.15193 (accessed 15 July 2024).

Rituximab has been shown to activate the complement pathway in humans and monkeys. Therapeutic activity and clinical response to rituximab depend on C1q, which is a fundamental element of the complement pathway. Activation of the complement cascade results in the production of soluble complement fragments, namely C3a and C5a, which in turn activate neutrophils and other inflammatory cells. Rituximab-induced PG may be a result of classical complement pathway hyperactivity [8].

2.2 Anti-CD20 antibodies

B-lymphocyte antigen CD20 is an activated-glycosylated phosphoprotein that is expressed on the surface of all B-cells. CD20 is involved in the regulation of trans-membrane Ca2+ conductance and also plays critical roles in cell-cycle progression during human B cell proliferation and activation. Increased expression of CD20 has been detected in patients with certain types of B-cell lymphoma and leukaemia [9].

Identification of various roles of CD20 led to the development of different monoclonal antibodies (ie, rituximab, ofatumumab, obinutuzumab and ocrelizumab) to treat a variety of diseases, such as cancer and autoimmune diseases [9]. These anti-lymphocyte monoclonal antibodies bind to CD20 transmembrane antigen on lymphocytes initiating immunologic reactions that mediate B-cell lysis [10].

2.2.1 Approved products

Obinutuzumab, ocrelizumab, ofatumumab and rituximab are the anti-CD20 antibodies approved in New Zealand (Table 1).

Table 1: Anti-CD20 antibody products approved in New Zealand, by active ingredient

Product name **Sponsor**	**Dose form** **Strength(s)**	**Approval date**	**Status**	**Funding**
Obinutuzmab (ATC: L01FA03)				
Gazyva Roche Products (NZ) Ltd	Concentrate for infusion 1000mg/40mL	13/11/2014	Consent given	Community: special authority SA2155 Hospitals: restrictions checklist RS1919
Ocrelizumab (ATC: L04AG08)				
Ocrevus Roche Products (NZ) Ltd	Concentrate for infusion 300mg/10mL	21/12/2017	Consent given	Community: special authority SA2273 Hospitals: restrictions checklist RS1997
Ofatumumab (ATC: L01FA02)				
Kesimpta Novartis NZ Ltd	Solution for injection 20mg/0.4mL	29/09/2022	Not available	Not funded
Rituximab (ATC: L01FA01)				
MabThera[a] Roche Products (NZ) Ltd	Concentrate for infusion 10 mg/mL	11/03/1999	Consent given	Community: special authority SA1976 Hospitals: restrictions checklist RS1785
Ristova Roche Products (NZ) Ltd	Concentrate for infusion 10mg/mL	10/10/2013	Not available	Not funded
Ritemvia Celltrion Healthcare NZ Ltd	Concentrate for infusion 100mg/10mL, 500mg/50mL	15/08/2019	Not available	Not funded
Riximyo Sandoz NZ Ltd	Concentrate for infusion 10mg/mL	01/11/2018	Consent given	Community: special authority SA2233 Hospitals: restrictions checklist RS1973
Ruxience Pfizer NZ Ltd	Concentrate for infusion 10mg/mL, 500mg/50mL	19/08/2021	Not available	Not funded
Truxima Celltrion Healthcare NZ Ltd	Concentrate for infusion 100mg/10mL, 500mg/50mL	15/08/2019	Consent given	Not funded

a. Mabthera is the innovator rituximab product, and the others are biosimilars.

Sources: Medsafe Product/Application Search and PHARMAC Community Schedule and Hospital Medicines List (accessed 12 July 2024).

Comment

Ofatumumab (Kesimpta) is the only approved anti-CD20 antibody that has no marketed products in NZ. There is no published data sheet for this product.

2.2.2 Usage data

The Pharmaceutical Data Web Tool does not have community usage data for obinutuzumab or rituximab, presumably as these medicines are administered in hospitals.

In Pharmac's Top 20 list of hospital medicines by gross spend for 2022/23, rituximab was ranked third ($8.9 million) behind infliximab ($52.63 million) and aflibercept ($16.53). Ocrelizumab ($2.84 million) was number 12 on the list.

Ocrelizumab was funded on 1 December 2019 for relapsing remitting multiple sclerosis (RRMS). The eligibility criteria for RRMS was widened on 1 March 2021 and 1 July 2022, and primary progressive MS (PPMS) was funded from 1 October 2023. Table 2 shows community usage data for ocrelizumab from 2019 to 2022 (ie, excludes hospitals). Use has increased in line with the widened funding.

Table 2: Ocrelizumab community dispensings, 2019 to 2022

Year	Initial dispensings (excludes repeats)		Dispensings (includes repeats)	
	NumDisps	NumPpl	NumDisps	NumPpl
2019	11	10	11	10
2020	345	219	391	219
2021	585	350	630	350
2022	826	466	886	466

NumDisps: Number dispensed; NumPpl: people who received a dispensing.

Source: Te Whatu Ora. 2023. *Pharmaceutical Data web tool* version 24 August 2023 (data extracted from the Pharmaceutical Collection on 08 June 2023). URL: https://tewhatuora.shinyapps.io/pharmaceutical-data-web-tool/ (accessed 12 July 2024).

2.2.3 Indications, dosing and mechanism of action

2.2.3.1 Obinutuzumab [11]

- In combination with chlorambucil, indicated in patients with previously untreated chronic lymphocytic leukaemia (CLL).
- In combination with chemotherapy followed by obinutuzumab maintenance, indicated for patients with previously untreated advanced follicular lymphoma.
- In combination with bendamustine followed by obinutuzumab maintenance, indicated for patients with indolent non-Hodgkin's lymphoma (iNHL) who did not respond to, or who progressed during or up to 6 months after treatment with rituximab or a rituximab-containing regimen.

Dosing varies according to the indication (and clinical guidelines), but 6 to 8 cycles are given, as IV infusion, with each cycle lasting 21 or 28 days. Maintenance therapy is given once every 2 months until disease progression or for up to 2 years.

Obinutuzumab specifically targets the extracellular loop of the CD20 transmembrane antigen on the surface of non-malignant and malignant pre B and mature B lymphocytes, but not haemopoietic stem cells, pro B cells, normal plasma cells or other normal tissue. Obinutuzumab induces direct cell death and mediates antibody dependent cellular cytotoxicity (ADCC) and antibody dependent cellular phagocytosis (ADCP) through recruitment of FcγRIII positive immune effector cells. In addition, obinutuzumab mediates a low degree of complement dependent cytotoxicity (CDC).

2.2.3.2 Ocrelizumab [12]

Ocrelizumab is indicated for adult patients with:

- relapsing forms of multiple sclerosis to suppress relapses and disease progression (clinical and subclinical disease activity)
- primary progressive multiple sclerosis to delay disease progression and reduce deterioration in walking speed.

The initial 600mg dose is administered as two separate IV infusions (300mg each) given two weeks apart. Subsequent doses are administered as a single 600mg infusion every 6 months (minimum interval 5 months).

Ocrelizumab is a recombinant humanised monoclonal antibody that selectively targets CD20-expressing B-cells. Its action in multiple sclerosis is not fully understood although is presumed to be related to the reduction in the number and function of CD20-expressing B-cells. Following cell surface binding, ocrelizumab selectively depletes CD20-expressing B-cells through antibody-dependent cellular phagocytosis, antibody-dependent cellular cytotoxicity, complement-dependent cytotoxicity and apoptosis.

2.2.3.3 Ofatumumab

- Ofatumumab is indicated for relapsing-remitting multiple sclerosis, to delay the progression of physical disability and reduce the frequency of relapse [13].

Ofatumumab is a fully human anti-CD20 monoclonal antibody. The binding of ofatumumab to CD20 induces lysis of CD20+ B-cells, primarily through complement-dependent cytotoxicity, and to a lesser extent through antibody-dependent cell-mediated cytotoxicity. Ofatumumab has also been shown to induce cell lysis in both high and low CD20 expressing cells. CD20-expressing T cells are also depleted by ofatumumab [14].

Comment

Kesimpta is not marketed in New Zealand and the data sheet is not published, so dosing information is not provided.

2.2.3.4 Rituximab [15]

Indications

Rituximab is indicated for non-Hodgkin's lymphoma, chronic lymphocytic leukaemia (CLL), rheumatoid arthritis, granulomatosis with polyangiitis (Wegener's) (GPA) and microscopic polyangiitis (MPA) as follows:

- CD20 positive previously untreated low-grade or follicular, B-cell non-Hodgkin's lymphoma in combination with chemotherapy
- CD20 positive, relapsed or chemoresistant low-grade or follicular, B-cell non-Hodgkin's lymphoma
- CD20 positive diffuse large B-cell non-Hodgkin's lymphoma in combination with chemotherapy
- maintenance treatment of CD20 positive, low grade or follicular, B-cell non-Hodgkin's lymphoma
- in combination with chemotherapy for patients with CLL
- in combination with methotrexate for patients with severe active rheumatoid arthritis who have had an inadequate response or intolerance to other disease modifying agents
- in combination with glucocorticoids for the induction of remission of patients with severely active GPA and MPA.

Dose

Dosing and treatment duration depends on the indication (and clinical guidelines). Rituximab is given by IV infusion.

Low-grade or follicular non-Hodgkin's lymphoma

For initial treatment

- Rituximab monotherapy - 375mg/m^2 body surface area given once weekly for 4 weeks.
- Rituximab plus any chemotherapy - 375mg/m^2 body surface area per cycle for 6 to 8 cycles (21 or 28 days per cycle).

Retreatment following relapse

- Rituximab 375mg/m^2 body surface area given once weekly for 4 weeks.

Maintenance treatment

- Rituximab 375mg/m^2 body surface area once every 2 or 3 months until disease progression or for up to 2 years (8–12 infusions).

Diffuse large B-cell non-Hodgkin's lymphoma

- Rituximab 375 mg/m^2 body surface area plus CHOP (cyclophosphamide, doxorubicin, prednisone and vincristine) chemotherapy, for 8 cycles.

CLL

- Rituximab 375 mg/m^2 body surface area + chemotherapy for first treatment cycle, followed by rituximab 500 mg/m^2 body surface area + chemotherapy for each subsequent cycle, for a total of 6 cycles.

Rheumatoid arthritis

A course is two rituximab 1000mg infusions, with the second infusion given two weeks after the first. Further courses as needed; the majority of patients receive further therapy 6–12 months after the previous course.

GPA and MPA

- Rituximab 375 mg/m^2 body surface area administered once weekly for 4 weeks.

Mechanism of action

Rituximab is a chimeric mouse/human monoclonal antibody that binds specifically to the transmembrane antigen CD20 on B-lymphocytes. This initiates immunologic reactions that mediate B-cell lysis. Possible mechanisms of cell lysis include complement-dependent cytotoxicity, antibody-dependent cellular cytotoxicity and induction of apoptosis. *In–vitro* studies have also demonstrated that rituximab sensitises drug-resistant human B–cell lymphoma lines to the cytotoxic effects of some chemotherapeutic agents.

2.3 Prescribing information – pyoderma gangrenosum

2.3.1 New Zealand

Pyoderma gangrenosum is not listed in any of the NZ data sheets. There are also no warnings or ADRs for skin reactions in the obinutuzumab (Gazyva) or ocrelizumab (Ocrevus) data sheets.

The rituximab (MabThera + Riximyo) data sheets include information about severe skin reactions in sections 4.4 and 4.8.

4.4 Warnings

Non-Hodgkin's lymphoma and chronic lymphocytic leukaemia patients

Skin Reactions

Severe skin reactions such as toxic epidermal necrolysis and Stevens-Johnson syndrome, some with fatal outcome, have been reported (see section 4.8). If signs and symptoms suggestive of a severe skin reaction occur, with a suspected relationship to MabThera, treatment should be permanently discontinued.

Rheumatoid arthritis (RA), Granulomatosis with polyangiitis (Wegener's) (GPA) and Microscopic polyangiitis (MPA)

Skin Reactions

Severe skin reactions such as toxic epidermal necrolysis and Stevens-Johnson syndrome, some with fatal outcome, have been reported (see section 4.8). If signs and symptoms suggestive of a severe skin reaction occur, with a suspected relationship to MabThera, treatment should be permanently discontinued.

4.8 Undesirable effects

Post-marketing experience

Non-Hodgkin's lymphoma and chronic lymphocytic leukaemia

Skin and appendages: Severe bullous skin reactions including some fatal cases of toxic epidermal necrolysis and Stevens-Johnson syndrome have been reported rarely.

Rheumatoid arthritis, Granulomatosis with Polyangiitis (Wegener's) (GPA)/ and Microscopic Polyangiitis (MPA) Patients

Skin and subcutaneous tissue disorders: Toxic epidermal necrolysis and Stevens-Johnson syndrome, with fatal outcome in some cases, have been reported very rarely.

2.3.2 International

Table 3 summarises international prescribing information. Pyoderma gangrenosum is included in the prescribing information in Switzerland for all anti-CD20 antibody products, and in the US for ocrelizumab and rituximab only. Table 4 shows the relevant PG text in the Swiss and US prescribing information (by active ingredient).

Table 3: Summary of international prescribing information, by country/jurisdiction and active ingredient

	Active ingredient			
Country/Jurisdiction	**Obinutuzumab**	**Ocrelizumab**	**Ofatumumab**	**Rituximab**
Australia	No	No	No	No
UK	No	No	No	No
Europe	No	No	No	No
Switzerland	**Yes**	**Yes**	**Yes**	**Yes**
USA	No	**Yes**	No	**Yes**
Canada	No	No	No	No

Sources (accessed 12 July 2024): Australia: TGA eBusiness Services Product and Consumer Medicine Information; UK: MHRA Products; Europe: EMA Medicines - EPAR documents; Switzerland: refdata portal (translated using Google translate); FDA: Drugs@FDA: FDA-Approved Drugs; Canada: Drug Product Database online query

Table 4: PG – Swiss and US prescribing information, by active ingredient

Active	Switzerland	USA
Obinutuzumab	**Gazyvaro** (September 2023) Warnings and precautionary measures *Skin reactions* Severe skin reactions such as toxic epidermal necrolysis (Lyell's syndrome), Stevens-Johnson syndrome and pyoderma gangrenosum have been observed with other anti-CD 20 antibodies. Should such an event occur, discontinuation of treatment should be considered.	
Ocrelizumab	**Ocrevus** (October 2023) Warnings and precautionary measures *Skin reactions* Cases of pyoderma gangrenosum have been described under treatment with Ocrevus. Other serious skin reactions such as toxic epidermal necrolysis (Lyell syndrome) and Stevens-Johnson syndrome have also been observed with other anti-CD20 antibodies. A skin biopsy is helpful in differentiating different types of skin reactions and determining subsequent treatment. Should such an event occur, discontinuation of treatment should be considered. Side effects *Pathologies of the skin and subcutaneous tissue* Not known (frequency cannot be estimated from the available data): pyoderma gangrenosum* (see «Warnings and precautions»). *Observed in post-marketing experience.	**Ocrevus** – PG added 18/8/2023 6 Adverse Reactions 6.3 *Postmarketing Experience* Skin: Pyoderma gangrenosum
Ofatumumab	**Kesimpta** (August 2023) Warnings and precautionary measures *Skin reactions* With the use of other anti-CD20 antibodies, severe skin reactions such as toxic epidermal necrolysis (Lyell's syndrome), Stevens-Johnson syndrome and pyoderma gangrenosum have been observed. If such an event occurs, discontinuation of treatment should be considered.	
Rituximab	**Mabthera** (October 2023), **Truxima** (December 2023), **Rixathon** (December 2023) Warnings and precautionary measures *Skin reactions* Serious skin reactions such as toxic epidermal necrolysis, Stevens-Johnson syndrome and pyoderma gangrenosum have been reported, some of which were fatal (see "Undesirable effects"). If such an event occurs and there is a suspicion of a correlation with [*product name*], treatment must be stopped permanently. Side effects *Pathologies of the skin and subcutaneous tissue* Not known: pyoderma gangrenosum.	**Rituxan** – PG added 25/11/2019 **Truxima** – PG added 18/12/2019 **Ruxience** – PG added 26/5/2020 6.4 Postmarketing Experience Skin: severe mucocutaneous reactions, pyoderma gangrenosum (including genital presentation).

Sources: Switzerland: refdata portal (translated using Google translate); FDA: Drugs@FDA: FDA-Approved Drugs

3 SCIENTIFIC INFORMATION

3.1 Published literature

Based on PubMed search for pyoderma gangrenosum [and]:

- each medicine individually (although there were no results for obinutuzumab or ofatumumab)
- anti-CD20 antibodies.

For rituximab-induced PG, observational studies, systematic reviews, reviews and case report/series were identified. For ocrelizumab, only case reports were identified. This section also includes 2 papers that describe treating PG with rituximab.

3.1.1 Drug-induced PG

3.1.1.1 Hillen et al. 2022. Rituximab and pyoderma gangrenosum: an investigation of disproportionality using a systems biology-informed approach in the FAERS database [16]

Objective To determine whether rituximab is disproportionally associated with pyoderma gangrenosum using a systems biology-informed approach.

Methods Adverse event reports were extracted from the US Food and Drug Administration Adverse Event Reporting System (FAERS) from 1 January 2013 to 30 September 2020.

Pyoderma gangrenosum was identified by a report of "Pyoderma Gangrenosum" (MedDRA Code = 10037635). Comparator ADRs included all other ADRs excluding skin conditions [System Organ Class categorisation of skin and subcutaneous tissue disorders]. This approach was employed to ensure competing or similar adverse events were removed from the baseline ADR counts to minimise misclassification. Adverse drug reactions were removed from the analysis if PG was the indication for any medicines taken by the patient prior to their report.

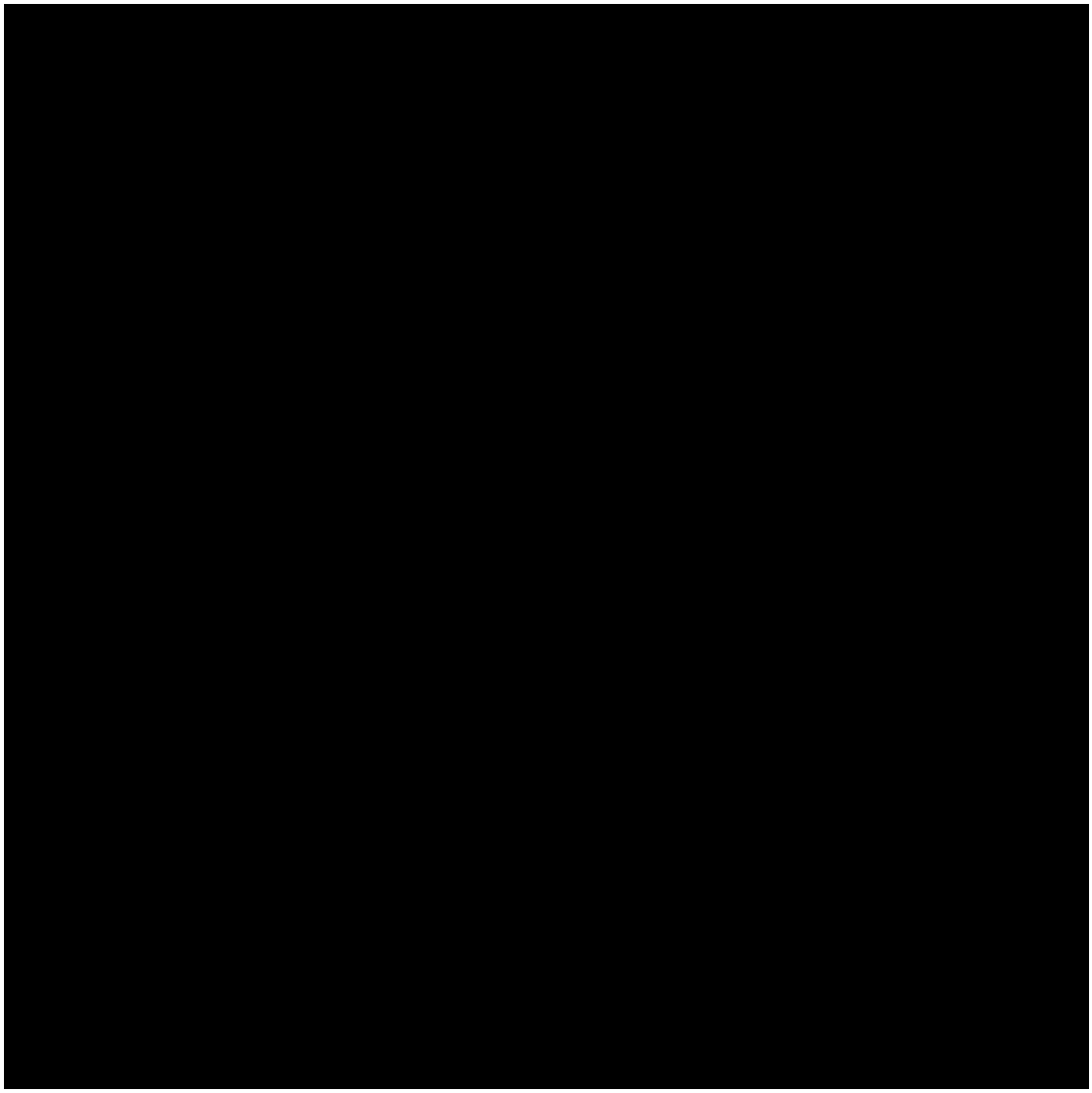
The authors used fuzzy string matching to optimise capture of medicine names (unlike ADRs and indications, these are not standardised). Data were limited to medicines that were listed as "primary suspect" to the ADR. Records were also limited to the last case version of the report (case id). Patient demographics and indications for rituximab were linked via the primary id corresponding to the last case version for each case id. Each list of comparator medicines was validated, prior to analysis, by clinical pharmacists.

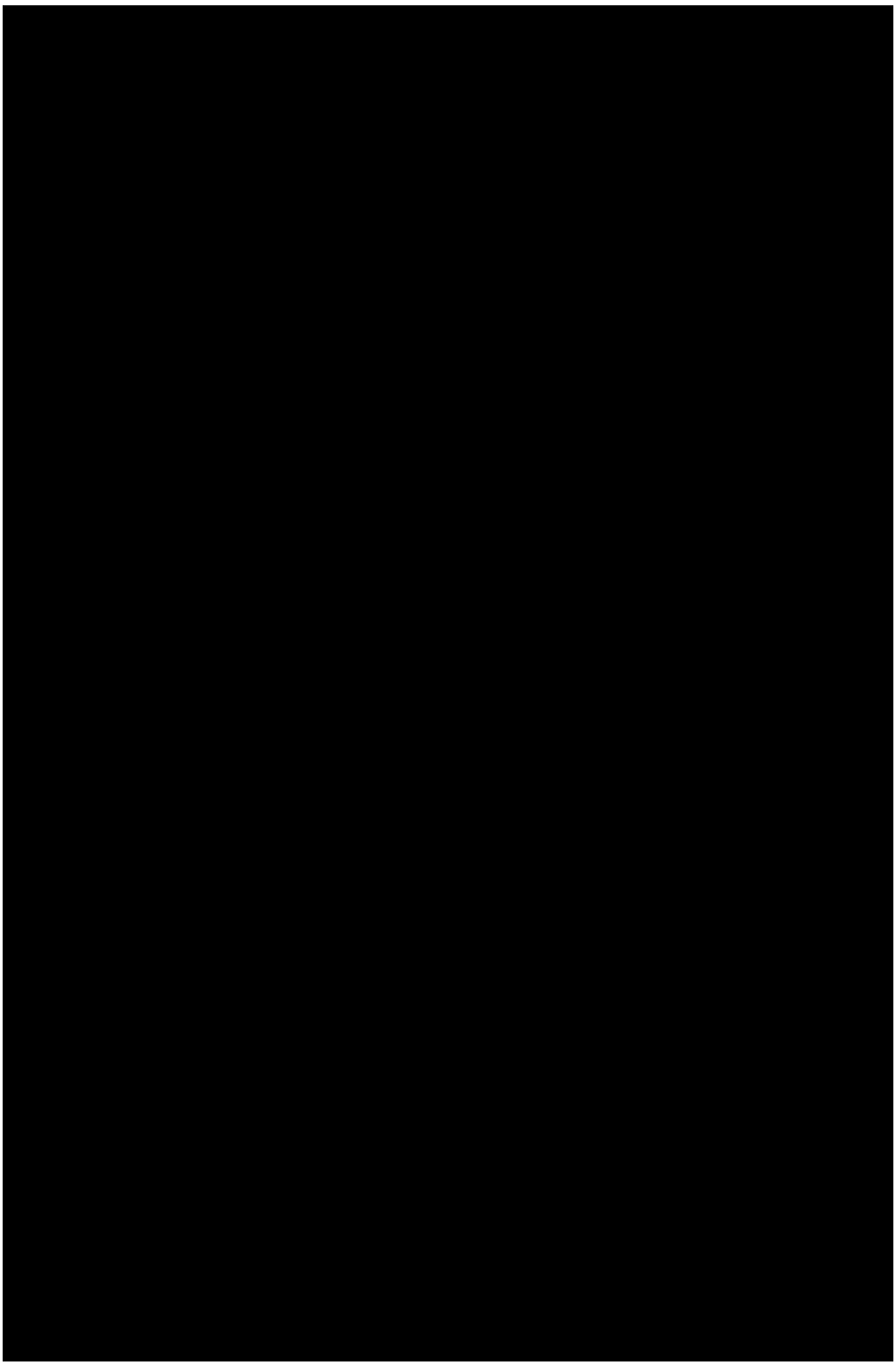
The Bayesian Confidence Propagation Neural Network Information Component was used to test for disproportionality. All medicine-outcome pairs where there were at least three reports were considered, and a potential signal was identified when the ratio scale Information Component (RSIC) estimate was >2 and the corresponding 95% confidence interval (CI) lower bound was >1 (significant at the $\alpha = 0.05$). A systems biology informed approach was used for choosing comparator groups to determine if the association varied according to chemical properties (monoclonal antibodies vs all other medicines), pharmacological action (CD20 inhibitors versus all other medications) or clinical indication (autoimmune disease and all other indications) (Table 5).

Table 5: Modified systems biology approach to choosing a comparator for the disproportionality analysis in FAERS

Results There were 1,105 reports of PG in the FAERS database, of which rituximab was the primary suspect in 32 cases and PG was not the indication for treatment (Table 6). The median age for rituximab PG cases and all other medicines was 48 and 51 years, respectively. For reports where sex was recorded, 100% of rituximab PG cases and 61.5% of all other medicines PG cases were female. PG cases were observed in every year of the study period.

Table 6: Report characteristics of PG cases in FAERS





There was an increased association of PG with rituximab compared with all other medicines (Figure 4 and Table 7). No association was observed when the comparator was either monoclonal antibodies or CD20 antagonists. PG was associated with rituximab for multiple sclerosis, rheumatoid arthritis and non-Hodgkin's lymphoma.

Figure 4: Signal detection estimates (ratio scale information component [RSIC]) of rituximab versus other comparators for pyoderma gangrenosum

Table 7: Adverse event counts for analyses

Limitations Underreporting and a lack of clinical details. Demographic details for age, sex, duration of treatment, comorbidities, re-challenge and de-challenge were missing for many cases, and this may influence the study outcomes. In addition, the preferred terms for outcome used in this study may not have captured all cases. Indication was missing from 155 reports, of these, 97% were in the non-rituximab cohort. The study used spontaneous ADR reporting data, which is limited by awareness of reporting, and also the skill level in diagnosing PG. The study may have underestimated the overall numbers of PG occurring in the community.

Conclusions Pyoderma gangrenosum was reported more frequently with rituximab compared with all other medicines. The varying results when restricting medicines for the same condition suggest the potential for confounding by indication. Post-market surveillance of biologic medicines in FAERS should consider a multi-faceted approach, particularly when the outcome of interest is associated with the underlying immune condition being treated by the medicine of interest.

Comment

Given the study is based on spontaneous ADR reports, the results should be interpreted with caution.

3.1.1.2 Lytvyn et al. 2022. Onset of pyoderma gangrenosum in patients on biologic therapies: A systematic review [17]

Objective: To summarise clinical outcomes of paradoxical PG onset in patients on biologic therapy.

Methods: The authors conducted MEDLINE and EMBASE searches using PRISMA guidelines. Articles were included if they involved patients who developed PG after biologic therapy initiation and had an observational or experimental study design. A descriptive analysis was conducted due to considerable heterogeneity of the included studies. The authors assessed the quality of the evidence using the Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence. Level 5 is the lowest level of evidence and was used for case reports in this systematic review. Level 4 was used for retrospective studies and case series. The quality of the included studies was assessed in relation to patient selection, ascertainment, causality, and data reporting using a tool proposed by Murad et al [18]. The authors used the Naranjo criteria to assess the probability of causation between the biologic and PG. A Naranjo score of 0 indicated doubtful association of PG with drug, a score of 1 to 4 indicated possible association, a score of 5 to 8 denoted probable association, and score of 9 or greater indicated a definite association.

Results: Twenty-three articles were identified, including 57 patients. The majority of studies included in this systematic review were the lowest level of evidence on the Oxford scale (level 5; 19/23 were observational case reports) and the remaining studies were level 4 (case series 3/23, retrospective study 1/23). Assessment of patient selection, ascertainment, causality, and data reporting in the included studies indicated that 4/23 studies contained good evidence, whereas the remaining 19/23 were fair.

The age ranged from 24 to 82 years (mean 51.3 years). Of the 57 patients, 10.5% were men (n = 6/57), 82.5% were women (n = 47/57), and the sex of 7.0% of patients was not reported (n = 4/57). Table 8 on the following page summarises the PG reactions reported during treatment with the different biologics.

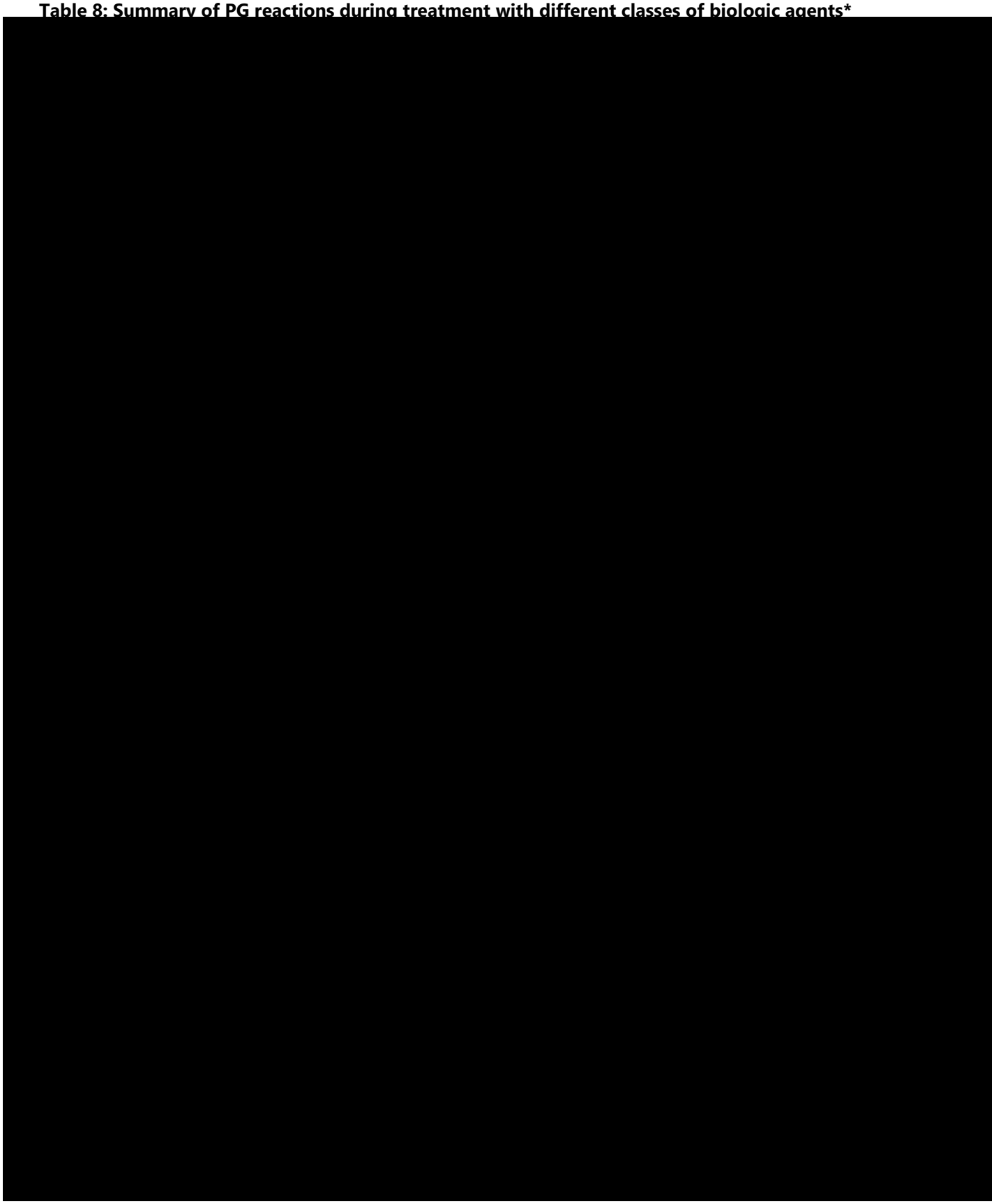
Of the included patients, 71.9% (n = 41/57) noted PG onset after initiating rituximab. PG was diagnosed between 1 month 10 days and 10 years after initiation of rituximab therapy (mean, 16.6 months). Indications for rituximab included conditions that may increase the baseline risk of PG (non-Hodgkin lymphoma, rheumatoid arthritis, juvenile idiopathic arthritis, granulomatosis with polyangiitis). Rituximab was discontinued in 43.9% of patients, continued in 2.4% and not reported in 53.7% of patients. Complete resolution of PG was reported in 17.1% of patients, partial resolution in 4.9% and not reported in 78.0% of patients. The most common medications used to resolve rituximab-associated PG were intravenous immunoglobulins, oral corticosteroids and antibiotics, with an average resolution time of 3.3 months. PG recurred in one patient upon resumption of rituximab, was reported not to recur in another, with the remaining cases not reporting data on recurrence.

Proposed mechanism: Rituximab can arrest neutrophil maturation and activate the NLRP3 inflammasome. Rituximab may also activate T cells by cross-presentation of apoptotic B cells via dendritic cells with subsequent vascular damage or secondary to prolonged B-cell lymphopenia. The resulting immune dysregulation of neutrophils and T cells may manifest as PG. Further investigations are required to determine the mechanisms involved and whether PG is indeed a serious mucocutaneous reaction in a very small proportion of patients on rituximab therapy.

Limitations: Observational studies with small sample sizes and heterogenous data, limiting the collected data and generalisability of the reported findings. The mean Naranjo score indicated only a possible adverse drug reaction (range, 2.0-4.0 in each drug class), so it may be difficult to conclude causality between medication use and PG onset. There were no re-challenge tests performed so it is unclear whether biologic use was related to the onset of PG. Most patients included in this review had comorbidities that may have increased their risk of developing PG. Insufficient control of the preexisting condition indicated for biologic use may have contributed to PG onset. Alternatively, PG onset could be idiopathic and independent from the preexisting condition or the biologic use.

Conclusions: Further investigations are warranted to determine whether PG onset is associated with underlying comorbidities, the use of biologic agents, or a synergistic effect. Nevertheless, PG may develop in patients on rituximab or TNF-α inhibitors, suggesting the need to monitor and treat such adverse effects.

Table 8: Summary of PG reactions during treatment with different classes of biologic agents*



[redacted]

Comments

The mean Naranjo score for the rituximab articles was 3.6, indicating a possible association of rituximab with PG. However, these articles are case reports, case series and retrospective chart reviews and the authors assessed them as evidence levels 4 and 5 on the Oxford scale (with level 5 being the lowest level of evidence). For the quality appraisal, 4/7 rituximab articles were assessed as Good (Aggarwal, Dixit, Maloney, Selva-Nayagam) and 3/7 were assessed as Fair (Georgakopoulos, Vikse, Walsh).

3.1.1.3 Croitoru et al. 2022. Clinical manifestations and treatment outcomes of pyoderma gangrenosum following rituximab exposure: A systematic review [26]

Aim: This systematic review of cases and observational studies aims to describe clinical features and outcomes of patients who developed PG during rituximab therapy.

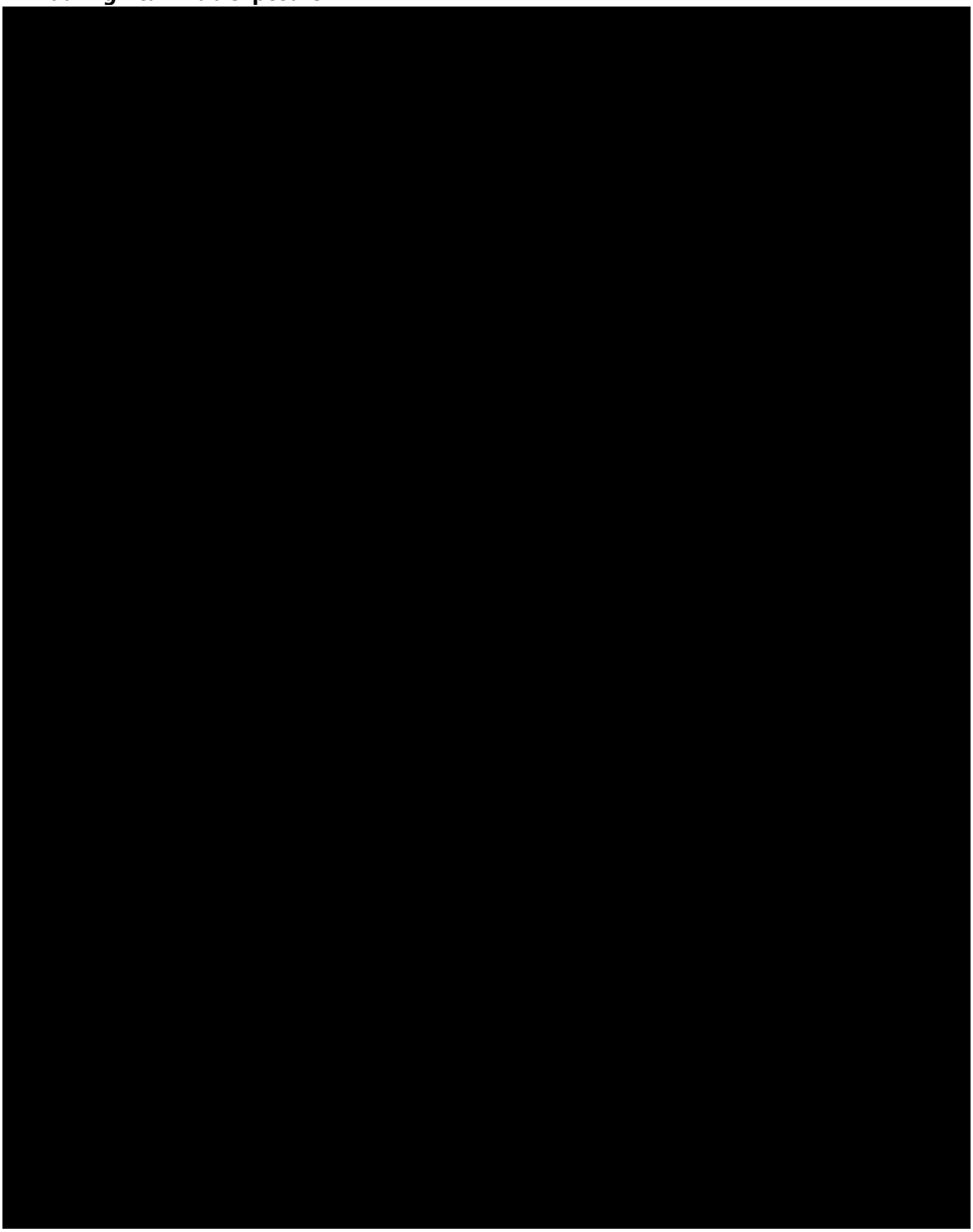
Methods: The protocol was developed according to Preferred Reporting of Systematic Reviews and Meta-Analyses and registered on PROSPERO (CRD42021239938). The authors searched Medline and Embase up until 3 June 2021. The inclusion requirements were development of PG during rituximab treatment and compatible histology or dermatologist consultation. Of the 173 articles retrieved, 11 met the inclusion criteria, with 16 cases of new-onset PG included (Table 9).

Table 9: List of included articles and contributory number of cases

[redacted]

Results: The mean age of the 16 cases was 53.1 years (standard deviation 18.3 years), and most were female (14/16) (Table 10). Common comorbidities were haematologic malignancy and autoimmune conditions. The mean duration of treatment (time to onset) was 40.9 months, and ulcerative PG was the most prevalent form. All female cases reported vulvovaginal PG. Corticosteroids and IVIG were the most commonly used treatments. There were 12 cases that reported subsequent rituximab management, and all of them indicated discontinuation of rituximab. Of the 12 cases that discontinued treatment, 9 reported a complete response to treatment by an average time of 9.7 months (standard deviation 3.2 months).

Table 10: Demographical and clinical features of patients presenting with pyoderma gangrenosum during rituximab exposure



[redacted]

The authors note that the review is limited to case reports and series with limited follow-up, although all cases included reported histology and/or a dermatology consultation. They assessed the cases using the Naranjo adverse reaction scale, and 15/16 scored 'probable' (Table 11).

Table 11: Probability assessment of rituximab-induced PG based on the Naranjo Adverse Drug Reaction Probability Scale

[redacted]

The authors note that there appears to be a clear vulvovaginal site preference for PG in the setting of rituximab exposure. This was seen across a broad spectrum of diseases associated diseases, both autoimmune and neoplastic, suggesting a true drug association. Mechanistically, the widely variable onset after drug initiation (months to years) may suggest an atypical T-cell activation and neutrophil response to local antigenic stimulation following B-cell depletion and apoptosis; however the pathogenesis is unknown.

Conclusions: Practitioners should consider the association between vulvovaginal PG and rituximab in women presenting with genital ulceration and on rituximab therapy.

Comments

This systematic review was published as a one-page letter to the editor in the Research Letters section of the Journal of the American Academy of Dermatology. It does not appear to be a completed study, although the supplementary materials could be downloaded (these are the source for Tables 9–11). The Prospero record (where the systematic review is registered) has not been updated to say that the study is completed. There is no mention of a risk of bias analysis or study limitations.

The authors assessed the 16 cases against the Naranjo scale and 15/16 recorded a score of probable (range 5-8; Table 11 above – the individual scores for each case not provided). However, 6 of the 11 articles in this review (representing 9 cases) were also assessed by Lytvyn et al (Walsh, Dixit, Selva-Nayam, Vikse, Georgakopoulos, Maloney) and the average Naranjo score was 3.56, indicating a possible rather than probable association (range 2–5).

The authors state that the articles were extracted up to 3 June 2021. However, the Parrotta article is included, which was first published online in December 2022, with a final publication date of February 2023.

3.1.1.4 Haber et al. 2021. Paradoxical neutrophilic dermatosis induced by biologics and immunosuppressive drugs: A systematic review [32]

Methods: The authors performed a systematic literature review, using Pubmed, Medline, and Embase databases and searching for all articles on paradoxical drug reaction (PDR) and drug side effects presenting as Sweet Syndrome (SS) or pyoderma gangrenosum (PG). There were no limits on publication date, participant age, sex, or nationality. Papers published in English or French were included.

Results: Forty-two articles were included, comprising a total of 84 patients. Of the 84 patients, 55 (65%) experienced paradoxical PG with a mean age of 35 and a male-to-female ratio of 1:2.5. Rituximab was the suspect medicine in 76% of the 55 cases, and infliximab (9%), etanercept (4%), adalimumab (4%), golimumab (2%), secukinumab (2%), and certolizumab (2%) for the remaining cases. Mean time to onset was 6 months in paradoxical PG. Similar to the classic presentations of SS and PG, the clinical presentations of neutrophilic PDR were mostly cutaneous with rare systemic involvement.

Rituximab-induced PDR may be linked to neutrophil activation or maturation, to prolonged B-cell lymphopenia, and to a dysregulated cytotoxic T-cell response.

The culprit medication was stopped in 94% of the PG and SS patients (79/84 cases), of whom 85% had complete and 15% had partial responses. Resolution was observed 2 to 90 days after drug discontinuation (median 14 days). After the drug was discontinued, 44 patients (95%) required additional systemic or topical treatment. Four patients were maintained on the culprit medication with favourable response (3 at the same initial dose, 1 at a reduced dose). One patient was re-challenged with half the initial dose with no recurrence of the neutrophilic dermatosis (ND).

Conclusions: The authors recommend the discontinuation of the drug as a first therapeutic step and the addition of systematic steroids or cyclosporine for severe or resistant cases. Re-challenge with the same drug at a reduced dosage or frequency of dosing can be considered on a case-by-case basis and only if the drug cannot be stopped.

Because ND can be associated with many of the included underlying diseases, some uncertainty remains concerning the causal relationship between these ND and the drug exposure. With the increasing use of biologics and immunosuppressant drugs, paradoxical neutrophilic dermatosis should not be overlooked. Early diagnosis and management of these reactions is paramount to improving patient outcomes.

Comments

Note that this paper describes SS and PG (2 common presentations of neutrophilic dermatosis (ND)), but the summary above focuses only on PG, where possible.

As with the Croitoru paper described above, this systematic review was published as a one-page letter to the editor in the Research Letters section of the Journal of the American Academy of Dermatology. It does not appear to be a completed study, and the only supplementary material was a document showing the stepwise approach in article selection. The 42 articles included in the review were not cited, and the case characteristics were not provided. There is no mention of levels of evidence, risk of bias assessment or study limitations.

3.1.1.5 Aggarwal. 2020. Pyoderma gangrenosum adverse event with Rituximab use: A postmarketing pharmacovigilance analysis [25]

Aim: To analyse whether a statistically significant signal exists between rituximab and pyoderma gangrenosum in the Food and Drug Administration Adverse Event Reporting System (FAERS).

Methods: A disproportionality analysis was carried out on FAERS cases from 1 January 2004 to 31 March 2019. Cases reports that contained the medicinal product "Rituximab" or "Rituxan" or "Mabthera" were included. The term "pyoderma gangrenosum" was included in the database search for pyoderma gangrenosum adverse events. Frequentist methods of relative reporting ratio (RRR), reporting odds ratio (ROR), and proportional reporting ratio (PRR) and the Bayesian-based Information Component (IC) were used in order to assess the adverse event signal.

For IC, a statistically significant signal is detected if the IC_{025} metric, a criterion indicating the lower bound of the 95% two-sided confidence interval of the IC, is >0. For ROR, a lower 95% CI of ROR >1 indicates a statistically significant signal. For PRR, a statistically significant signal is when the number of cases is ≥3, PRR was greater than 2, and Chi-squared >4.

Results: There were 32 cases identified, of these, 26 were in females, 2 in males and the remaining 4 unknown. Patient ages ranged from 24 to 82 years (mean 52.11, standard deviation 17.20). The most common indications were non-Hodgkin's lymphoma and rheumatoid arthritis (Table 12).

Table 12: Indications for administration of rituximab in FAERS case reports, 1 January 2004 to 31 March 2019

One case was reported as fatal and 2 as life-threatening. Of the 13/32 cases that reported a drug action, all reported withdrawal of rituximab.

Disproportionality analysis results are shown in Table 13. The lower 95% CI of the information component was 0.97, the lower 95% CI of ROR was 2.18, the PRR was 3.09 and Chi-squared was 42.16, which indicates a statistically significant signal.

Table 13: Disproportionality measures for rituximab and pyoderma gangrenosum in FAERS, 1 January 2004 to 31 March 2019

The signal is supported by six case reports in the literature (Maloney [24], Georgakopoulos [23]and Dixit [20]) that describe 14 patients who developed vulvovaginal pyoderma gangrenosum after rituximab administration.

The authors also noted 3 case reports where PG was treated with rituximab. One case report involved treatment of only pyoderma gangrenosum (Donmez [33]) and two case reports each contained a patient being treated for pyoderma gangrenosum and granulomatosis with polyangiitis (Murthy [34], DaCunha [35]), as shown in Table 14.

Table 14: Case reports in literature of treatment of pyoderma gangrenosum with rituximab

Limitations: FAERS is a passive reporting system and neither every use of the drug nor every adverse event is reported to the database, making it unsuitable for calculating incidence of an adverse event associated with a drug. Analysis of the FAERS database points to a signal between a drug and an adverse event. FAERS reports cannot prove causality.

Conclusions: Based on pharmacovigilance analysis of real world adverse events reported to FDA, and supported by published case reports, rituximab was found to have a statically significant signal with pyoderma gangrenosum. Further investigation is needed in order to assess whether a causal relationship exists. When administering rituximab, clinicians should monitor for the occurrence of symptoms representing pyoderma gangrenosum.

Comment

As noted by the authors, spontaneous reports can only identify signals and not confirm causality.

Of the 3 papers cited for treatment of PG, only 1 was a true case of PG (DaCunha – see section 3.1.2.2). The other 2 papers were associated with GPA and rituximab is indicated for treatment of GPA.

3.1.1.6 Vikse et al. 2019. Tolerability and safety of long-term rituximab treatment in systemic inflammatory and autoimmune diseases [36]

Aim: To evaluate the long-term safety and tolerability of rituximab treatment for systemic inflammatory and autoimmune diseases (SIADs).

Methods: This was a retrospective, single-centre observational study that included all patients ≥16 years treated with rituximab for SIADs at the Clinical Immunology Unit at Stavanger University in Norway. The electronic medical records were reviewed, and data concerning indication and duration of rituximab treatment, prior and concurrent immunosuppressive therapy, and adverse events such as infections requiring hospitalization, dysgammaglobulinemia and end organ damage, were collected. 100 patients were identified, but 25 were excluded as treatment duration was <2 years and 5 were excluded due to co-existing malignancies. No patients were lost to follow-up and no patients declined inclusion, leaving 70 patients for inclusion.

Results: Of the 70 included patients, 58.6% were female, and the median age at initiation of rituximab treatment was 51.5 years (range 16–81) (Table 15). Rituximab was administered for a wide range of diseases and conditions, with granulomatosis with polyangiitis (GPA), primary Sjögren's syndrome (pSS) and systemic lupus erythematosus (SLE) being the most common. One patient was being treated for PG.

Table 15: Indication for rituximab treatment

The median number of rituximab cycles was 10 (IQR 8), ranging 6–24. Rituximab was scheduled at 0 and 2 weeks, followed by 6-month intervals. Hence, 10 cycles equate to a median treatment duration of approximately 54 months (range 30–138 months). At the end of the observational period, 35 patients (50.0%) had discontinued rituximab treatment.

Three patients (4.3%) received rituximab as monotherapy, and the most frequent concurrent immunosuppressive agents were corticosteroids (prednisolone: 63 patients, 90.0%; methylprednisolone: 21 patients 30%) and methotrexate (24 patients, 34.3%).

Infections and persistent dysgammaglobulinemia were the most common adverse events, occurring in 34.3% and 25.7% of patients, respectively (Table 16). End organ damage occurred in two patients, with one case presenting as pyoderma gangrenosum. The PG case was reported to have a diagnosis of GPA. The treating physician considered PG to represent an adverse event of rituximab rather than a manifestation of the underlying disease. The patient was hospitalised for 90 days with multi-organ failure requiring long-term vasopressor therapy and mechanical ventilation. Rituximab was discontinued.

Table 16: Complications in the observation period

[redacted]

Limitations: Heterogeneity of the population, both in terms of underlying disease, as well as prior and concurrent immunosuppressive therapy. Differences in follow-up time, retrospective nature and single centre design.

Conclusions: This study presents observational data with long treatment duration. It demonstrates that long-term rituximab treatment is relatively well tolerated, and that no cumulative side effects were observed.

Comments

This study was included as the PG case was mentioned. This case is also described in the Vikse et al study from 2017 [22].

The study focused on overall safety of rituximab, and of the 70 included patients only 1 experienced PG. This patient was reported to have GPA, which is an approved indication in NZ. However, the NZ dosing schedule for GPA is 375 mg/m^2 body surface area once weekly for 4 weeks, whereas the 2017 case report states this patient was in complete remission of the GPA and was receiving biannual rituximab (1000mg) and low-dose prednisolone (5mg) daily.

There was also one patient with PG who was treated with rituximab – although no further detail about this patient was provided.

3.1.1.7 Yamout. 2018. Safety and efficacy of rituximab in multiple sclerosis: A retrospective observational study [37]

Aim: To evaluate the efficacy and safety of rituximab in multiple sclerosis in a clinical practice setting.

Methods: Clinical data for all adult patients with multiple sclerosis (MS) treated with off-label rituximab at a single MS centre in Lebanon between March 2008 and April 2017 were retrospectively collected from medical charts. Patients were included if there was ≥3 months of follow-up and excluded if they had been treated with rituximab for other medical conditions or had a lack of follow-up data. Rituximab treatment consisted of a higher loading dose (2000mg IV) subdivided into 2 infusions given at a 2-week interval, then single 1000mg infusions every 6-12 months. The main efficacy outcomes assessed were annualized relapse rate (ARR) and proportion of patients free from relapses, disability progression, or magnetic resonance imaging (MRI) activity. All adverse events occurring during rituximab treatment were also recorded.

Results: A total of 89 rituximab-treated patients were included: 59 relapsing-remitting MS (RRMS) and 30 progressive MS (PMS). Patients were treated with 1000 or 2000 mg rituximab IV every 6–12 months for a mean duration of 22.2 ± 24.8 months. The subjects were 65.2% females with a mean age of 40.5 ± 12.3 years and a mean disease duration of 7.9 ± 6.2 years. Only 10 (11.2%) patients received rituximab as their first disease-modifying drug (DMD), while all the others switched from other therapies, mainly interferon-beta (IFN) and fingolimod. The most common reason for switching to rituximab was persistent disease activity despite treatment with other DMDs (87.3% of patients).

A total of 64 adverse events (AEs) (71.9%) were recorded, with the most common being infusion-related reactions in 25.8% of patients, all mild in nature (Table 17). Two patients experienced serious AEs requiring surgical interventions: pyoderma gangrenosum vaginalis with perianal abscess and fistula, and an increase in the size of a meningioma.

Table 17: Adverse events and serious adverse events

Limitations: Potential for selection bias due to being a single-centre retrospective study. Small sample size.

Conclusions: Rituximab was well-tolerated and effective in reducing relapse rate and stabilising disease in relapsing-remitting and progressive MS patients in our real-world clinical practice setting.

Comments

As with the Viske study above, this study by Yamout was included because PG was a reported adverse event. However, rituximab was used off-label, so generalisability to the approved indications is limited.

3.1.1.8 Case reports and case series

Table 18 below is a summary of the rituximab cases and Table 19 the ocrelizumab cases.

Eleven papers were identified for rituximab, representing 16 cases. Most of these cases were discussed in the section above. Almost all reports of rituximab-associated PG were in females (14/16). The average age of the 16 cases was 53.3 years (median 57.5 years, range 24–87 years). Almost all cases (15/16) completely recovered from PG, and 1 case partially recovered. Action with rituximab was reported in 11/16 cases, 10 of which reported discontinuation. The eleventh case (Walsh) reported that the patient completed therapy with rituximab following PG resolution, with no recurrence of PG (negative rechallenge).

Two papers were identified for ocrelizumab, representing 2 cases (Breneman and Klumpp), both in females. The Breneman case had a history of rituximab treatment for multiple sclerosis. The authors could not say with certainty whether the PG was due to ocrelizumab, rituximab, MS or a combination of these factors, but suspected that ocrelizumab may have partly triggered it.

Table 18: Summary of rituximab and pyoderma gangrenosum case reports and case series

Study	Age Sex	RTX indication	Other medicines/treatment Comorbidities	Clinical PG presentation	TTO	PG management + outcome Action taken with RTX
Parrotta et al 2023 [28]	27 F	RRMS	RRMS initially treated with glatiramer acetate followed by dimethyl fumarate	1st: several months of vaginal discharge, dyspareunia and vaginal ulceration, plus fever 2nd: pain from adnexa to rectum, tachycardia, fever, leukocytosis, elevated lactic acid levels	3 y	1st: Broad-spectrum antibiotics, topical clobetasol, oral prednisone 2nd: Surgery, oral prednisone, IVIG – full recovery Switched from RTX to fingolimod
	25 M	RRMS	RRMS initially treated with glatiramer acetate followed by interferon beta 1a Neurogenic bladder with frequent urinary tract infections	Fever, cloudy urine, diarrhoea, deep abscess of left buttock, multiple abscesses identified on MRI	7 y	Surgical debridement, prostate resection – did not improve Parenteral steroids, IVIG – recovered Switched from RTX to fingolimod
Sotzen et al 2021 [31]	67 F	RA	RA previously treated with infliximab, etanercept, adalimumab, and abatacept. Switched to RTX and MTX.	Exquisitely tender suppurative vaginitis for 10 months	3 y	IVIG, prednisone – recovered Stopped RTX
	87F	RA	RA previously treated with MTX, sulfasalazine, hydroxychloroquine, cyclosporine, adalimumab, etanercept and abatacept	Painful vaginal ulcers for 1 year, fistula	6 y	Prednisone, dapsone – recovered (although later died due to natural causes) Switched from RTX to tocilizumab
Jones et al 2020 [27]	55 F	RA	NR	Post-menopausal bleeding and copious discharge, ulcerative inflammation on biopsy	NR	Clobetasol and metered foam pessaries – recovered Stopped RTX
Georgakopoulos et al 2018 [23]	59 F	RA	RA controlled with MTX, hydroxychloroquine and low-dose prednisone. Diffuse large B-cell lymphoma treated with 6 rounds of R-CHOP and radiation therapy. 2-years after completing R-CHOP and radiation, started on RTX for ongoing RA management	Perianal and labial cysts, green vaginal discharge, full-thickness ulcers of the bilateral buttocks, and vulvovaginal region	12 mo	Prednisone, sulfasalazine, intralesional triamcinolone – recovered Stopped RTX
Maloney et al 2018 [24]	24 F	SLE	SLE initially treated with hydroxychloroquine, then mycophenolate mofetil added but discontinued. Switched to RTX	Painful labial, perineal, and perianal ulcers and abscesses, 2 fistulas	2 mo	Prednisone, cyclosporine, tacrolimus ointment – recovered Action with RTX NR

Study	Age Sex	RTX indication	Other medicines/treatment Comorbidities	Clinical PG presentation	TTO	PG management + outcome Action taken with RTX
Roche et al 2018 [38]	64 F	Follicular B-cell lymphoma	8 cycles of chemotherapy for lymphoma, including RTX	Painful vulvo-vaginal and perianal erosions that rapidly progressed to frank ulceration with extensive destruction of vulvar architecture	NR	Corticosteroids, cyclosporine – recovered Action with RTX NR
Vikse et al 2017 [22]	29 F	GPA	Tracheostomy for tracheal granulomas Septic peritonitis, respiratory failure	Copious vaginal discharge, extensive vulvovaginal ulceration	5 y	Methylprednisolone, IVIG – recovered Stopped RTX
Selva-Nayagam* et al 2015 [21]	74 F	B-cell NHL	IVIG for NHL	Severe purulent discharge for 2 years, deep vulvar ulcers	NR	10% hydrocortisone cream, intravaginal and on vulva – recovered Action with RTX NR
Dixit et al 2015 [20]	62 F	B-cell NHL	R-CHOP for NHL	Pain, discharge, deep vulvar ulceration, anal discomfort	6 y	Prednisolone, azathioprine but switched to IVIG (as has BK virus and CMV) – partial recovery Action with RTX NR
	50 F	B-cell NHL	R-CHOP initially for NHL then just RTX	Vulvovaginal itch, discharge, discomfort, pain	3 mo	IVIG, prednisolone – recovered Stopped RTX
	56 F	B-cell NHL	NR	Heavy vaginal discharge, painful vulvar ulceration	18 mo	Prednisolone with no response, switched to IVIG – recovered Stopped RTX
	60 F	B-cell NHL	NR	Dysuria, vaginal burning, heavy discharge	~10 y	Prednisolone not tolerated by patient, switched to high-dose MTX – recovered Stopped RTX
Solovan et al 2013 [29]	62 M	CLL	Surgery for renal cell carcinoma, L-thyroxine for hypothyroidism	Non-healing ulcer following nephrectomy for renal cell carcinoma	NR	Initially broad spectrum antibiotics then prednisolone after PG diagnosis – recovered Action with RTX NR
Walsh 2011 [19]	51 F	Follicular NHL	NHL previously treated with CHOP, then R-CHOP following relapse	Ulceration of vulva, destruction of labia majora, extension into vagina with discharge, necrosis and haemorrhage	12 mo	Prednisolone, minocycline – recovered Following resolution, completed RTX with no recurrence of PG

CHOP: cyclophosphamide, doxorubicin (hydroxydaunomycin), vincristine (Oncovin), prednisolone; CLL: chronic lymphocytic leukaemia; F: female; GPA: granulomatosis with polyangiitis; IV: intravenous; IVIG: intravenous immunoglobulin; M: male; mo: month; MTX: methotrexate; NHL: non-Hodgkin's lymphoma; NR: not reported; PG: pyoderma gangrenosum; RA: rheumatoid arthritis; R-CHOP: rituximab, cyclophosphamide, doxorubicin (hydroxydaunomycin), vincristine (Oncovin), prednisolone; RRMS: relapsing remitting multiple sclerosis; RTX: rituximab; SLE: systemic lupus erythematosus; TTO: time to onset; y: years.

*Selva-Nayagam reported 6 cases, 4 of which were also published by Dixit and 1 by Walsh. Only the unique case is listed here.

Table 19: Summary of ocrelizumab and pyoderma gangrenosum case reports

Ocrelizumab						
Study	**Age Sex**	**Ocrelizumab indication**	**Other medicines/treatment Comorbidities**	**Clinical PG presentation**	**TTO**	**PG management + outcome Action taken with ocrelizumab**
Breneman et al 2022 [39]	55 F	RRMS	Initially treated with 3 years of RTX, then switched to ocrelizumab	Profuse, mucopurulent vaginal discharge, progressing to vulvar ulcerations with severe pain	6 mo	Prednisone, triamcinolone, methylprednisolone, IVIG, cyclosporine, clobetasol – recovered but continuing on monthly IVIG for 12 months Stopped ocrelizumab
Klumpp et al 2022 [40]	23 F	RRMS	Initially treated with natalizumab but switched to ocrelizumab due to infusion-related dyspnoea and drug eruption	Painful, inflamed vulvovaginal ulcerations from the vaginal labium to the perianal and gluteal area	2.5 y	IVIG, cyclosporine – recovered Stopped ocrelizumab

F: female; IVIG: intravenous immunoglobulin; M: male; mo: months; PG: pyoderma gangrenosum; RRMS: relapsing remitting multiple sclerosis; RTX: rituximab; TTO: time to onset; y: years.

3.1.2 Treating PG

3.1.2.1 Maronese et al. 2022. Pyoderma gangrenosum: An updated literature review on established and emerging pharmacological treatments [5]

Aim: To review established and emerging pharmacological treatments for PG.

Methods: Published studies were assessed against the Centre for Evidence Based-Medicine levels of evidence (Table 20).

Table 20: Levels of evidence for therapeutic studies adapted from the Centre for Evidence-Based Medicine

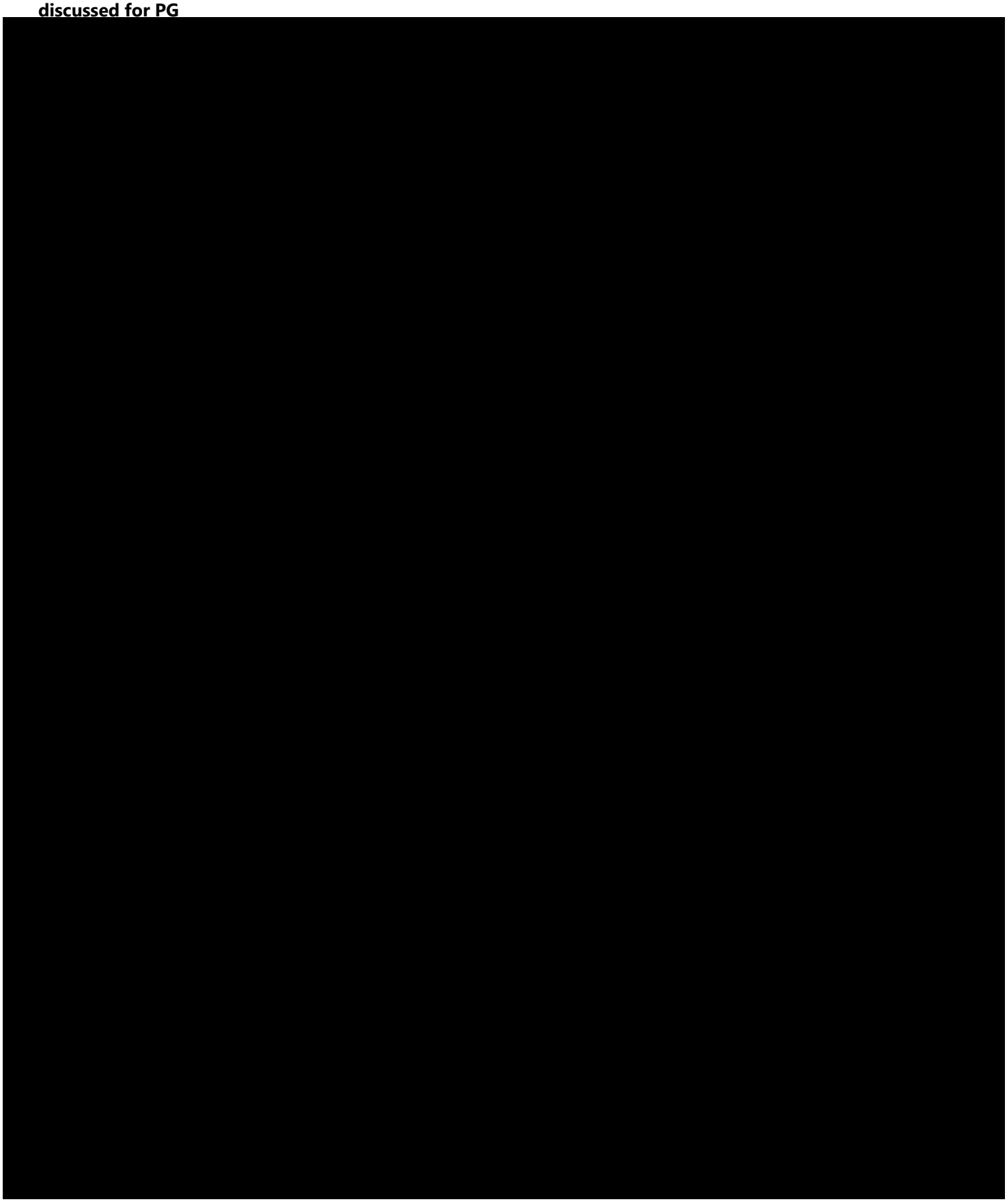
[redacted]

Results: Corticosteroids and cyclosporine (immunosuppressants) and infliximab (tumour necrosis factor inhibitor) had the highest level of evidence for reported treatment options (level 1B) (Table 21 on the following page). Rituximab (CD20 inhibitor) was assessed as evidence level 4.

For the evidence level review of CD20 inhibitors, the authors cite case reports from Sen [41], Murthy [34] and DaCunha [35]. Rituximab has been seen to improve PG-like ulcers in patients with associated granulomatous polyangiitis and refractory PG ulcers in those without an underlying comorbidity.

The authors note that conversely, a recent systematic review demonstrated that rituximab may be associated with vulvovaginal PG (Croitoru [26]), and it appears to be responsible for the majority of new-onset PG cases reported with biologic therapies (Lytvyn [17]).

Table 21: Posology, mechanism of action and current level of evidence for the main treatment options discussed for PG



Comments

There was no mention of the authors' search strategy for identifying articles for inclusion in the review, nor how the articles were assessed against the levels of evidence.

The Sen and Murthy cases describe treatment of PG-like ulcers in patients with GPA. Rituximab is approved in NZ for induction of remission of patients with severely active GPA. See below for the DaCunha case.

The systematic review for rituximab-induced PG cited by the authors was Croitoru, described above. And the citation for the majority of new-onset PG cases was Lytvyn, also described above.

3.1.2.2 Da Cunha et al. Pyoderma gangrenosum controlled with rituximab [35]

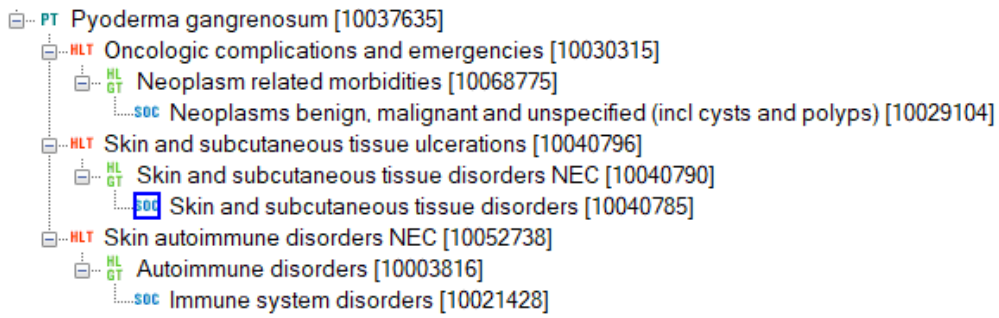
Case: This is a case report of a 24-year-old male patient with a 6-year history of recalcitrant ulcerative and vegetative PG, including involvement of two-thirds of his face. The patient's attempt at pain control led to narcotic addiction, depression and anxiety. No cause was identified, and the patient had been treated without success with oral and intravenous corticosteroids (including 6 years of prednisone), ciprofloxacin, minocycline, intralesional triamcinolone, mycophenolic acid, infliximab, adalimumab, acitretin, azathioprine, apremilast, radiation, and intravenous immunoglobulin. The patient was tapered off systemic corticosteroids over 1 year and rituximab was initiated. He noted significant improvement within 3 months and complete clearing at 6 months using 600mg of IV rituximab per week. He was advised to taper off rituximab but has not due to fear of relapse. He has been in remission for 10 months.

The authors note that this case was atypical in that it was the less common vegetative subtype of PG, prednisone over 6 years failed to prevent progression and the patient responded well to rituximab despite negative workup for underlying disease, including heme malignancy.

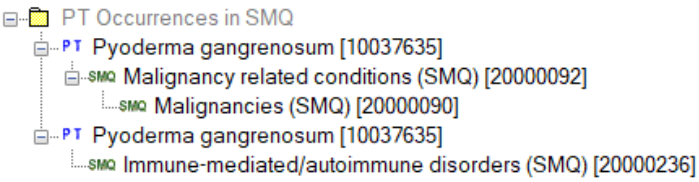
3.2 Spontaneous reports

Figure 5 below shows the MedDRA coding for PG (at the Preferred term [PT] level). PG fits within multiple System Organ Classes (SOCs), but the primary SOC is Skin and subcutaneous tissue disorders (shown by the blue square). PG is also coded within two Standardised MedDRA Queries (SMQs): Malignancies, and Immune mediated/Autoimmune disorders.

Figure 5: MedDRA coding for pyoderma gangrenosum



SOC Code	SOC Name	Primary SOC
10029104	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	N
10040785	Skin and subcutaneous tissue disorders	Y
10021428	Immune system disorders	N



3.2.1 New Zealand

There are no NZ reports for the Pyoderma gangrenosum PT in association with obinutuzumab, ocrelizumab, ofatumumab or rituximab.

Given that PG is difficult to diagnose, and the clinical presentation is ulcers, the search was extended to determine if any cases could potentially be PG. The extended search included reports for the medicines:

- in the Skin and subcutaneous disorders System Organ Class
- in both of the SMQs
- with ulcer PTs.

There were no relevant reports for obinutuzumab (and none for ofatumumab as it is not available in NZ). Five reports were identified with ulcer PTs, with 2 for ocrelizumab and 3 for rituximab (Table 22). Limited information was provided in the reports.

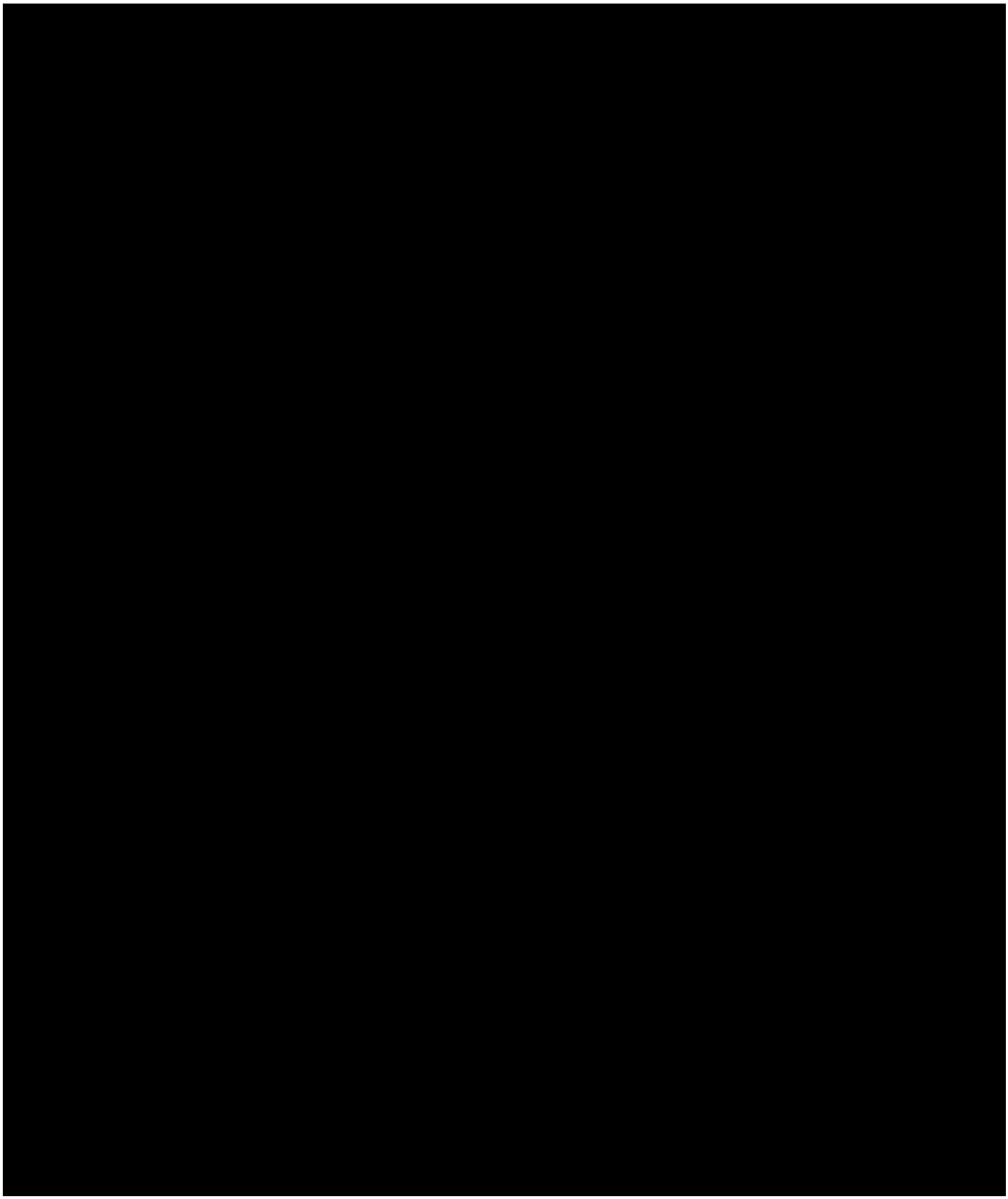
Table 22: NZ reports with rituximab and ocrelizumab that include ulcer preferred terms, as of 8 August 2024.
Suspect medicine(s) in bold

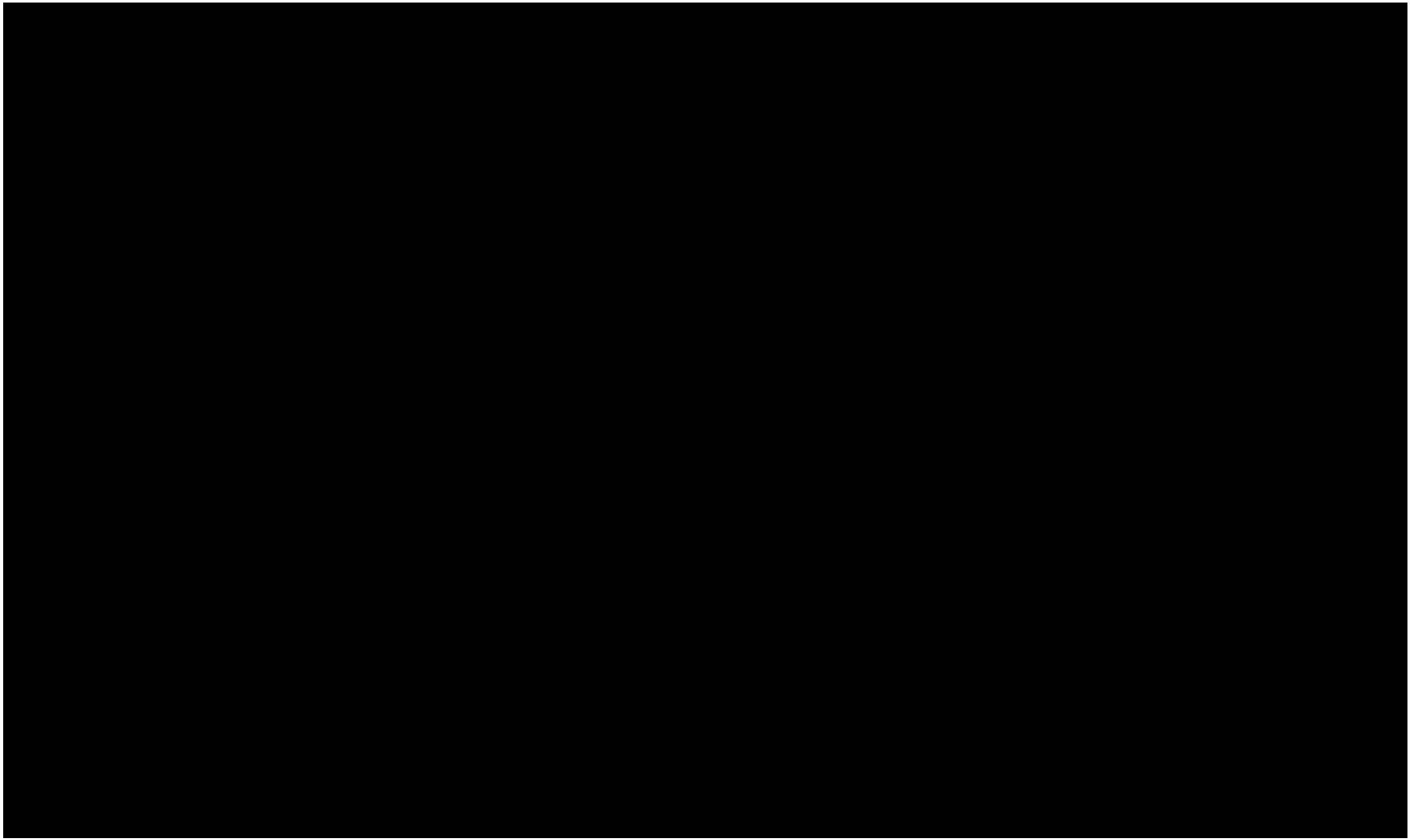
Report ID (date)	**Age Sex**	**Medicines,**			**Reactions**		
112258 (Jun 2014)	59 years Male	**Rituximab**,			Mouth ulceration		
120333 (Apr 2016)	40 years Female	**Rituximab**, **Ibuprofen**, **Methotrexate**,			Oesophageal ulcer		
142682 (Nov 2021)	59 years Male	**Rituximab**, **Sulfamethoxazole + Trimethoprim**, **Allopurinol**, Valaciclovir, Bendamustine, Entecavir, oral, Cetirizine, oral, Metoclopramide,			Mouth ulceration Rash pruritic Pyrexia		

Report ID (date)	**Age Sex** [redacted]	**Medicines,** [redacted]	[redacted]	[redacted]	**Reactions**	[redacted]	[redacted]
147532 (May 2023)	Male	**Ocrelizumab**		[redacted]	Gastric ulcer Anaemia	[redacted]	[redacted]
147986 (Jun 2023)	41 years Male	**Ocrelizumab**, [redacted] **Flucloxacillin**, [redacted] Neutral insulin, [redacted] Sertraline, [redacted] Lamotrigine, [redacted]	[redacted]	[redacted]	Infection Skin ulcer Abscess	[redacted]	[redacted]

Key: [redacted]

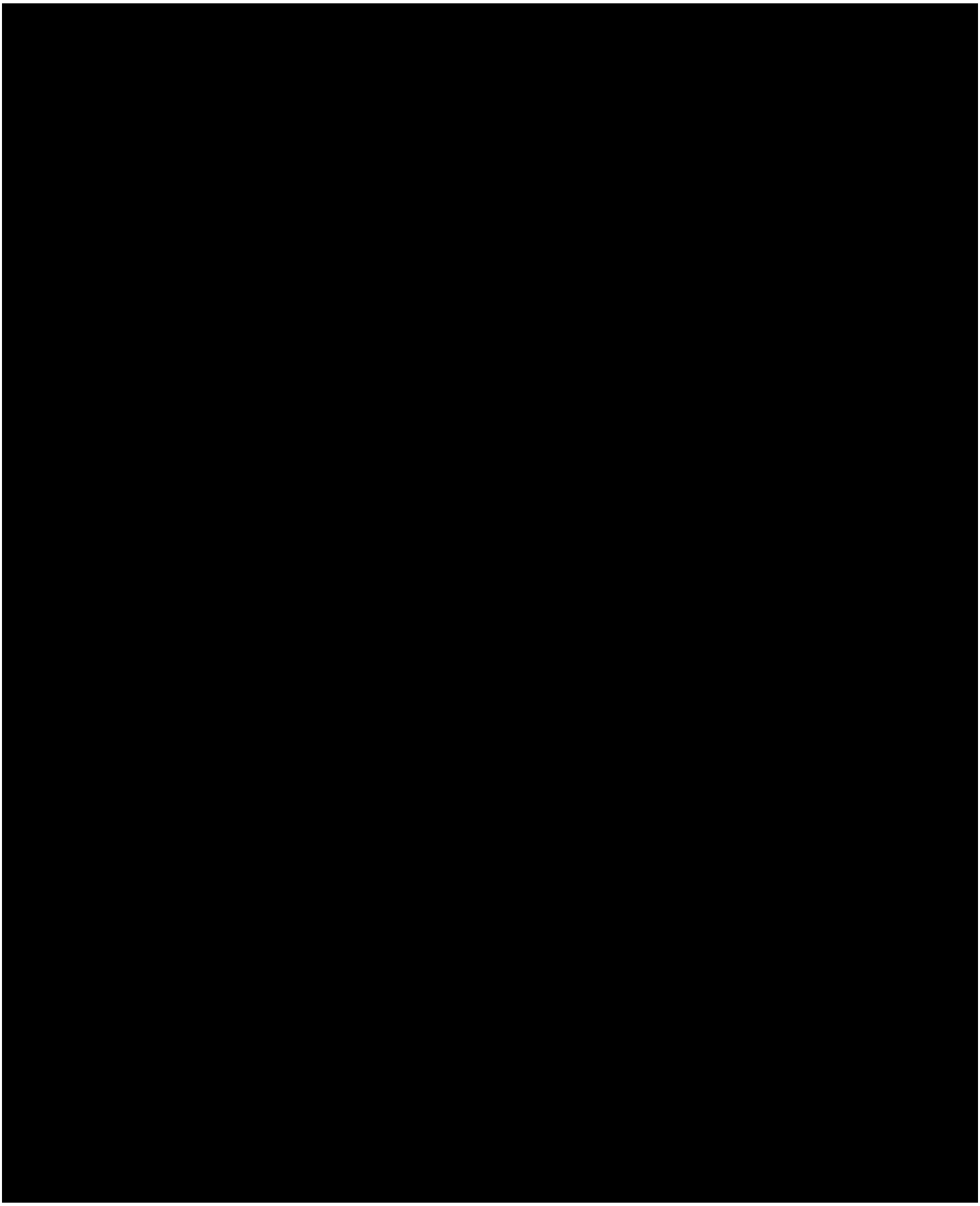
3.2.2 International (Vigilyze)





3.3 Company reports

[redacted]



4 DISCUSSION AND CONCLUSIONS

Pyoderma gangrenosum (PG) is a reactive non-infectious inflammatory dermatosis falling under the spectrum of the neutrophilic dermatoses. There are several subtypes, with 'classical PG' as the most common form in approximately 85% of cases. It presents as an extremely painful erythematous lesion which rapidly progresses to a blistered or necrotic ulcer. There is often a ragged undermined edge with a violaceous/ erythematous border.

PG is a rare disease, with an incidence of approximately 3 to 10 cases per million people per year. It can affect individuals of any age but is more common in those aged over 50 years. PG diagnosis is challenging due to its variable presentation, clinical overlap with other conditions, association with several systemic diseases, and absence of defining histopathologic or laboratory findings.

Up to 50% of cases have underlying systemic conditions, with inflammatory bowel disease, rheumatological disorders and haematological malignancies the most frequently associated conditions. Injury to the skin is a common trigger, and a surgical trigger is often misinterpreted as a wound infection.

Medicines have also been reported to trigger PG. Several mechanisms for drug-induced PG have been proposed, such as dysfunctional neutrophil migration and function, dysregulated inflammatory response, promotion of keratinocyte apoptosis and alteration of epigenetic mechanisms.

Anti-CD20 antibodies (rituximab, ofatumumab, obinutuzumab and ocrelizumab) treat a variety of diseases such as cancers and autoimmune diseases (eg, multiple sclerosis). They are anti-lymphocyte monoclonal antibodies that bind to CD20 transmembrane antigen on lymphocytes initiating immunologic reactions that mediate B-cell lysis.

PG has been reported in patients treated with anti-CD20 antibodies. Most reports are for rituximab, followed by ocrelizumab. However, the literature describing PG in association with anti-CD20 antibodies mostly consists of reviews of pharmacovigilance databases and case reports. The reported cases are almost all in women, all of whom experienced ulcerating vulvovaginal PG. There is disproportional reporting for rituximab and ocrelizumab in Vigilyze.

Conversely, rituximab has also been used to treat PG, although the quality of the evidence is poor.

PG is not listed in the NZ data sheets, although 2 rituximab products describe severe skin reactions. The Swiss regulator recently mandated updates to the Swiss prescribing information for all anti-CD20 antibodies. In the US, the prescribing information for rituximab products has included PG since 2019, and the US regulator recently mandated updates for ocrelizumab products.

5 ADVICE SOUGHT

The Committee is asked to advise:

- Whether there is evidence for an association between pyoderma gangrenosum and anti-CD20 antibodies as a class (obinutuzumab, ocrelizumab, ofatumumab, rituximab)?
  - If yes, are data sheet updates required?
- If there is no evidence for the class, is there evidence for an association between pyoderma gangrenosum and one or more anti-CD20 antibodies, and if so, which one(s)?
  - Are data sheet updates required for the specified anti-CD20 antibodies?
- Does the topic require further communication, other than MARC's remarks in *Prescriber Update*?

6 ANNEXES

[redacted]

7 REFERENCES

1. Oakley A and Dhawan G. 2015. Pyoderma gangrenosum. In: *DermNet* updated March 2022. URL: https://dermnetnz.org/topics/pyoderma-gangrenosum (accessed 7 March 2024).
2. George G, Deroide F and Rustin M. 2019. Pyoderma gangrenosum – a guide to diagnosis and management. *Clinical Medicine (London, England)* 19(3): 224-8. DOI: 10.7861/clinmedicine.19-3-224 (accessed 5 August 2024).
3. Ben Abdallah H, Fogh K, Vestergaard C, et al. 2021. Pyoderma gangrenosum and interleukin inhibitors: A semi-systematic review. *Dermatology* 238(4): 785-92. DOI: https://doi.org/10.1159/000519320 (accessed 17 June 2024).
4. Maverakis E, Ma C, Shinkai K, et al. 2018. Diagnostic criteria of ulcerative pyoderma gangrenosum: A Delphi consensus of international experts. *JAMA Dermatology* 154(4): 461-66. DOI: 10.1001/jamadermatol.2017.5980 (accessed 5 August 2024).
5. Maronese C, Pimentel M, Li M, et al. 2022. Pyoderma gangrenosum: An updated literature review on established and emerging pharmacological treatments. *American Journal of Clinical Dermatology* 23(5): 615-34. DOI: 10.1007/s40257-022-00699-8 (accessed 17 June 2024).
6. Qureshi A, Persaud K, Zulfiqar S, et al. 2021. Atypical Pyoderma gangrenosum: a case of delayed recognition. *Journal of Community Hospital Internal Medicine Perspectives* 11(2): 242-8. DOI: https://doi.org/10.1080/20009666.2020.1866250 (accessed 17 April 2024).
7. Na H, Yan H and CH P. 2023. Misdiagnosis of pyoderma gangrenosum increases medical costs and prolongs hospital stay: A case report (abstract only). *The International Journal of Lower Extremity Wounds* 22(2): 428-33. DOI: 10.1177/15347346211011870 (accessed 17 April 2024).
8. Wu B, Patel E and Ortega-Loayza A. 2017. Drug-induced pyoderma gangrenosum: a model to understand the pathogenesis of pyoderma gangrenosum. *British Journal of Dermatology* 177(1): 72-83. DOI: 10.1111/bjd.15193 (accessed 15 July 2024).
9. Payandeh Z, Bahrami A, Hoseinpoor R, et al. 2019. The applications of anti-CD20 antibodies to treat various B cells disorders. *Biomedicine and Pharmacotherapy* 109: 2415-26. DOI: https://doi.org/10.1016/j.biopha.2018.11.121 (accessed 7 March 2024).
10. New Zealand Formulary (NZF). 2024. *NZF v.141: Obinutuzumab* 1 March 2024. URL: https://nzf.org.nz/nzf_70375 (accessed 7 March 2024).
11. Roche Products NZ Limited. 2022. *Gazyva New Zealand Data Sheet* 21 July 2022. URL: https://www.medsafe.govt.nz/profs/Datasheet/g/GazyvaInfusion.pdf (accessed 17 April 2024).
12. Roche Products NZ Limited. 2022. *Ocrevus New Zealand Data Sheet* 12 August 2022. URL: https://www.medsafe.govt.nz/profs/datasheet/o/Ocrevusinf.pdf (accessed 17 April 2024).
13. Medsafe. 2024. *Medsafe Product Detail: Kesimpta* 29 September 2022. URL: https://www.medsafe.govt.nz/regulatory/ProductDetail.asp?ID=22430 (accessed 7 March 2024).
14. Novartis Ireland Limited. 2021. *Kesimpta European Summary of Product Characteristics* 26 March 2021. URL: https://www.ema.europa.eu/en/documents/product-information/kesimpta-epar-product-information_en.pdf (accessed 12 Juy 2024).
15. Roche Products NZ Limited. 2023. *MabThera New Zealand Data Sheet* 1 February 2023. URL: https://www.medsafe.govt.nz/profs/datasheet/m/Mabtherainf.pdf (accessed 17 April 2024).
16. Hillen B, Stanford T, Ward M, et al. 2022. Rituximab and pyoderma gangrenosum: an investigation of disproportionality using a systems biology-informed approach in the FAERS database. *Drug Real Word Outcomes* 9(4): 639-47. DOI: 10.1007/s40801-022-00322-6 (accessed 18 March 2024).
17. Lytvyn Y, Mufti A, Maliyar K, et al. 2022. Onset of pyoderma gangrenosum in patients on biologic therapies: A systematic review. *Advances in Skin & Wound Care* 35(8): 454-60. DOI: 10.1097/01.ASW.0000820252.96869.8e (accessed 17 June 2024).
18. Murad M, Sultan S, Haffar S, et al. 2018. Methodological quality and synthesis of case series and case reports. *BMJ Evidence Based Medicine* 23(2): 60-3. DOI: 10.1136/bmjebm-2017-110853 (accessed 21 August 2024).

19. Walsh M, Leonard N and Bell H. 2011. Superficial granulomatous pyoderma of the vulva in a patient receiving maintenance rituximab (MabThera) for lymphoma. *Journal of Lower Genital Tract Disease* 15(2): 158-60. DOI: 10.1097/LGT.0b013e3181eb30ff (accessed 16 July 2024).
20. Dixit S, Selva-Nayagam P, Hamann I, et al. 2015. Vulvovaginal pyoderma gangrenosum secondary to rituximab therapy. *Journal of Lower Genital Tract Disease* 19(1): e6-9. DOI: 10.1097/LGT.0000000000000043 (accessed 17 June 2024).
21. Selva-Nayagam P, Fischer G, Hamann I, et al. 2015. Rituximab causing deep ulcerative suppurative vaginitis/pyoderma gangrenosum. *Current Infectious Disease Reports* 17(5): 478. DOI: 10.1007/s11908-015-0478-5 (accessed 17 June 2024).
22. Vikse J, Rygh A, Kaisen K, et al. 2017. Life-threatening rituximab-induced pyoderma gangrenosum successfully treated with intravenous immunoglobulin. *Scandinavian Journal of Rheumatology* 46(5): 413-14. DOI: 10.1080/03009742.2016.1241298 (accessed 18 June 2026).
23. Georgakopoulos J, Rohekar G and Lovegrove F. 2018. A case of rituximab-induced pyoderma gangrenosum. *JAAD Case Reports* 4(10): 979-81. DOI: 10.1016/j.jdcr.2018.09.003 (accessed 17 June 2024).
24. Maloney C, Blickenstaff N, Kugasia A, et al. 2018. Vulvovaginal pyoderma gangrenosum in association with rituximab. *JAAD Case Reports* 4(9): 907-09. DOI: 10.1016/j.jdcr.2018.09.001 (accessed 17 June 2024).
25. Aggarwal A. 2020. Pyoderma gangrenosum adverse event with rituximab use: A postmarketing pharmacovigilance analysis. *Dermatologic Therapy* 33(2): e13221. DOI: 10.1111/dth.13221 (accessed 18 March 2024).
26. Croitoru D, Nathanielsz N, Seigel K, et al. 2022. Clinical manifestations and treatment outcomes of pyoderma gangrenosum following rituximab exposure: A systematic review. *Journal of the American Academy of Dermatology* 87(3): 655-6. DOI: 10.1016/j.jaad.2021.12.028 (accessed 17 June 2024).
27. Jones N, Azad J, Twigg J, et al. 2020. Vaginal pyoderma presenting as postmenopausal bleeding. *British Society for Skin Care in Immunosuppressed Individuals: Special Issue - Abstracts for the British Association of Dermatologists 100th Annual Meeting, Virtual Meeting* 183(S1): BI10. URL: https://doi.org/10.1111/bjd.19092(accessed 21 August 2024).
28. Parrotta E, Kopinsky H, Abate J, et al. 2023. It's not always an infection: Pyoderma gangrenosum of the urogenital tract in two patients with multiple sclerosis treated with rituximab. *Multiple Sclerosis and Related Disorders* 70(Feb): 104483. DOI: 10.1016/j.msard.2022.104483 (accessed 17 June 2024).
29. Solovan C, Smiszek R, Wickenhauser C, et al. 2013. Postoperative pyoderma gangrenosum in association with renal cell carcinoma and chronic lymphocytic leukemia. *Infectious Diseases and Therapy* 2(1): 75-80. DOI: 10.1007/s40121-013-0008-4 (accessed 21 August 2024).
30. Murray G, Tierney E, Tobin A-M, et al. 2021. *Fistulating vulvo-vaginal pyoderma gangrenosum associated with rituximab (Conference poster)* 15th Medical Dermatology Meeting British Association of Dermatologists 2021.
31. Sotzen J and Stratman E. 2021. Vulvovaginal pyoderma gangrenosum associated with rituximab use in 2 patients with rheumatoid arthritis. *JAAD Case Reports* 10(Apr): 75-77. DOI: 10.1016/j.jdcr.2021.02.013 (accessed 17 June 2024).
32. Haber R, Dib N, El Gemayel M, et al. 2021. Paradoxical neutrophilic dermatosis induced by biologics and immunosuppressive drugs: A systematic review. *Journal of the American Academy of Dermatology* 85(4): 1048-9. DOI: https://doi.org/10.1016/j.jaad.2021.02.035 (accessed 15 July 2024).
33. Donmez S, Pamuk O, Gedik M, et al. 2014. A case of granulomatosis with polyangiitis and pyoderma gangrenosum successfully treated with infliximab and rituximab (abstract only). *International Journal of Rheumatic Diseases* 17(4): 471-5. DOI: 10.1111/1756-185X.12274 (accessed 17 June 2024).
34. Murthy R, Jackson J, Chatham W, et al. 2016. Extensive pyoderma gangrenosum associated with granulomatosis with polyangiitis with both responsive to Rituximab (abstract only). *Journal of Clinical Rheumatology: practical reports on rheumatic and musculoskeletal diseases* 22(7): 393-5. DOI: https://journals.lww.com/jclinrheum/citation/2016/10000/extensive_pyoderma_gangrenosum_associated_with.16.aspx (accessed 21 August 2024).

35. DaCunha M, Siscos S, Downing M, et al. 2019. Pyoderma gangrenosum controlled with rituximab. *JAAD Case Reports* 5(7): 593-5. DOI: 10.1016/j.jdcr.2019.04.019 (accessed 17 June 2024).
36. Vikse J, Jonsdottir K, Kvaløy J, et al. 2019. Tolerability and safety of long-term rituximab treatment in systemic inflammatory and autoimmune diseases. *Rheumatology International* 39(6): 1083-90. DOI: 10.1007/s00296-019-04272-1 (accessed 17 June 2024).
37. Yamout B, El-Ayoubi N, Nicolas J, et al. 2018. Safety and efficacy of rituximab in multiple sclerosis: A retrospective observational study. *Journal of Immunology Research* 12(2018): 9084759. DOI: 10.1155/2018/9084759 (accessed 17 June 2024).
38. Roche L, Gulman C and O'Kane M. 2018. A case of genital pyoderma gangrenosum successfully treated with cyclosporine without relapse of established follicular lymphoma. *JAAD Case Reports* 4(5): 474-6. DOI: 10.1016/j.jdcr.2018.01.004 (accessed 15 July 2024).
39. Breneman A, Eber A, Haque H, et al. 2022. Vulvovaginal pyoderma gangrenosum in a patient treated with ocrelizumab for multiple sclerosis. *Journal of Lower Genital Tract Disease* 26(2): 189-91. DOI: 10.1097/LGT.0000000000000661 (accessed 18 June 2026).
40. Klumpp A, Luessi F, Engel S, et al. 2022. Ocrelizumab-induced vulvovaginal pyoderma gangrenosum in a patient with relapsing-remitting multiple sclerosis. *JAAD Case Reports* 10(Aug): 24-7. DOI: 10.1016/j.jdcr.2022.08.005 (accessed 19 June 2024).
41. Sen M, Dogra S, Rathi M, et al. 2016. Successful treatment of large refractory pyoderma gangrenosum-like presentation of granulomatosis with polyangiitis by rituximab. *International Journal of Rheumatic Diseases* 20(12): 2200-2202. DOI: https://doi.org/10.1111/1756-185X.12882 (accessed 22 August 2024).
42. Uppsala Monitoring Centre. 2016. *The UMC Measures of Disproportionate Reporting* URL: https://who-umc.org/media/164041/measures-of-disproportionate-reporting_2016.pdf (accessed 28 August 2024).