AWTTC
All Wales Therapeutics & Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

Rituximab for the treatment of pemphigus (excluding pemphigus vulgaris) and pemphigoid disease in adults and children (OW10)

May 2022

One Wales Interim Commissioning Decision

Rituximab for the treatment of adults and children with pemphigus (excluding pemphigus vulgaris) after failure of first-line treatments including steroids and steroid-sparing treatments and after failure of third-line treatments for pemphigoid disease including steroids and steroid-sparing treatments

Date of original advice: July 2017
Date of review: May 2022

The following One Wales Medicines Assessment group (OWMAG) recommendation has been endorsed by health board Chief Executives.

Rituximab can continue to be made available within NHS Wales for the second-line treatment of pemphigus (excluding pemphigus vulgaris) and fourth-line treatment of pemphigoid disease in adults and children whose disease has not responded to previous treatments including steroids and steroid-sparing agents.

Rituximab is not licensed to treat this indication and is therefore 'off-label'. Each provider organisation must ensure all internal governance arrangements are completed before this medicine is prescribed.

The risks and benefits of the off-label use of rituximab for this indication should be clearly stated and discussed with the patient to allow informed consent.

Providers should consult the relevant guidelines on prescribing unlicensed medicines before any off-label medicines are prescribed.

This advice will be reviewed after 12 months or earlier if new evidence becomes available.

Clinician responsibility
Clinicians will be obliged to collect and monitor patient outcomes. Evidence of clinical outcomes will be taken into consideration when reviewing the One Wales Medicines Assessment decision.

Health board responsibility
Health boards will take responsibility for implementing One Wales Medicines Assessment Group decisions and ensuring that a process is in place for monitoring clinical outcomes.

One Wales advice assists consistency of access across NHS Wales.

Starting and stopping criteria for rituximab for the treatment of pemphigus (excluding pemphigus vulgaris) and pemphigoid disease in adults and children

These criteria have been adapted from the NHS England Clinical Commissioning Policy document and the British Association of Dermatologists' (BAD) guidelines for the management of pemphigus vulgaris[1,2].

Starting criteria (pemphigus variants excluding vulgaris):
Rituximab may be considered after treatment failure with systemic corticosteroids and topical care. Systemic corticosteroid treatment failure is defined as continued disease activity or failure to heal despite three weeks of prednisolone (1.5 mg/kg/day).

Starting criteria (pemphigoid):
Rituximab is a fourth-line option alongside topical care and systemic corticosteroids. Systemic corticosteroids are a well-established and effective treatment for pemphigoid and should be used as first-line therapy, alongside topical care. In the event of corticosteroid treatment failure (defined as above), addition of a steroid-sparing immunosuppressant, either azathioprine or mycophenolate mofetil, may be considered as second line treatment, switching to the alternate as third-line treatment.

Patients who satisfy the eligibility criteria will be prescribed rituximab following consultation with the patient and/or carer taking into account potential adverse effects, cautions and contraindications. This is particularly relevant when considering the use of rituximab in frailer elderly patients and its side effects profile. This consultation should be recorded in the patient's notes.

Rituximab must only be used for treatment in specialised centres, or in collaboration with a specialised centre under the supervision of an expert multidisciplinary team.

The recommended rituximab treatment dose regimen for adults with variants of pemphigus or with pemphigoid is 1,000 mg rituximab followed by a second 1,000 mg dose two weeks later administered by intravenous infusion. Repeat courses may be given at up to six monthly intervals.

Continuing and stopping criteria:
Stopping criteria are based on the literature which suggests that it can take up to six months (but more often one to three months) for rituximab to induce complete remission, broadly defined as the absence of new blisters and healing of the majority (> 75%) of lesions (skin and mucosal) for at least two months, with continued remission. If disease control is achieved, further cycles of rituximab should not be given.

Relapse following a period of response to rituximab:
Benefit from a single cycle of rituximab may last 9–18 months or more. A second cycle may be considered in the case of relapse.

Treatment failure:
Treatment failure is defined as continued disease activity or failure to heal, measured up to six months after a cycle of rituximab. Subsequent treatment options may be considered by the team, both in the event of rituximab failing to achieve disease control and also based on assessment of individual patient need.

This is a summary of new evidence available and patient outcome data collected, to inform the review

Background: Pemphigus is a group of rare autoimmune conditions in which painful, fragile blisters occur on the skin and mucous membranes. Types of pemphigus include pemphigus vulgaris, pemphigus foliaceus and paraneoplastic pemphigus. Bullous pemphigoid (BP) is a similar blistering skin disease that tends to affect older people. An NHS England Clinical Commissioning Policy recommends rituximab for use in adults and children as an option to treat pemphigus or pemphigoid that has not responded to steroids and steroid-sparing agents. Based on unmet need to treat this cohort of patients rituximab was considered suitable for assessment through the One Wales process.

Licence status: Off-label use for this licensed medicine Rituximab (MabThera®), and three biosimilar medicines (Rixathon®, Ruxience® and Truxima®) are licensed in the UK for the treatment of moderate-to-severe pemphigus vulgaris. No submission to AWMSG has been made for any of these medicines. AWMSG issued a statement of advice for MabThera® in June 2019. Therefore, the use of rituximab to treat pemphigus vulgaris is not endorsed by One Wales, and this review applies only to other types of pemphigus and all types of pemphigoid.

Guidelines: European guidelines on the diagnosis and management of mucous membrane pemphigoid (MMP) state that rituximab may be recommended as a second-line treatment in severe MMP, and as third-line treatment in mild/moderate MMP refractory to conventional immunosuppressants.

Licensed alternative medicines or Health Technology Assessment advice for alternative medicines: no new medicines or HTA advice reported.

Effectiveness: A systematic literature search identified one systematic review of biological medicines to treat MMP and four relevant retrospective studies that included patients with BP, MMP or pemphigus foliaceus (PF) (See Appendix 1). The systematic review concluded that overall the data suggest that biological therapies, including rituximab, were promising treatment options for patients with high-risk MMP who are either not responsive to conventional therapies or are experiencing significant adverse effects but randomised clinical trials are needed. In the retrospective studies, most patients achieved complete or partial remission after rituximab treatment. In one retrospective review in patients with BP (Yoo et al., 2021), it was not clear if rituximab was given first-line, second-line or as a later treatment. The data were compared with a retrospective group who received conventional therapy; the number of patients treated with rituximab that were excluded from the analyses was not provided.

Safety: No relevant safety analyses identified in the repeat literature search.

Cost effectiveness: No relevant cost-effectiveness analyses identified in the repeat literature search.

Budget impact: No information on patient numbers has been provided.

Impact on health and social care services: Minimal.

Patient outcome data: No patient outcome data have been received.

Next review date: May 2023

References: a full reference list is available on request

Appendix 1:

Reference	Study details	Main results
Lytvyn et al. (2021)	**Systematic review** of biologic treatments for MMP. Identified 63 studies in 331 patients with MMP (with or without ocular involvement) or paraneoplastic MMP. Most patients previously treated with steroid-sparing immunosuppressants, corticosteroids or antibiotics. 112 patients received rituximab.	Complete remission of symptoms occurred in 70.5% of patients (79 of 112) on rituximab within 8.7 months, with a recurrence rate of 35.7% (40 of 112) in 1.9 years. Adverse events reported with rituximab were urinary tract infection (n = 5); severe infection with hypergammaglobulinaemia (n=3, 2 died); leukocytopenia (n = 3).
Retrospective studies		
Yoo et al. (2021)	48 patients with BP were treated with rituximab 1,000 mg two weeks apart at a referral hospital in South Korea. Compared with 168 patients with BP who did not receive rituximab taken from a study of mortality rates at 1, 2 and 5 years. Median follow-up period was 1.7 years for rituximab; 2.19 years for conventional therapy group.	In the rituximab cohort, remission rate during follow-up was 79% (38 of 48 patients) taking a median of 148 days. Relapse rate was 29% (11 of 38 patients who achieved remission) with a median time from remission to relapse of 5.6 months. The 1-year, 2-year and 5-year mortality rates were 14%, 17% and 25% (rituximab) and 19.5%, 29.1% and 58.0% (conventional therapy group). Survival rate was higher in the rituximab cohort than in the conventional therapy cohort over the follow-up period. Eight patients died whilst on rituximab therapy: infectious pneumonia (n = 5), aspiration pneumonia (n = 1), poor general condition (n = 1) unknown cause (n = 1). Five of whom died within 6 months.
Rashid et al. (2021)	A single-centre, observational study of patients with BP (n = 7) and MMP (n = 16) who were treated with rituximab and had previously failed conventional immunosuppressive therapies. Patients received rituximab 1,000 mg two weeks apart, followed by 500 mg at Months 6 and 12.	Disease control was achieved in 19 patients (83%): 6 with BP and 13 with MMP. Remission (partial or complete) was achieved in 17 patients (74%): 5 with BP and 12 with MMP. Two patients with BP and 5 with MMP achieved complete remission off therapy. Use of adjuvant immunosuppression or immunomodulators reduced from 21 patients at Month 0, to 17 at Month 6, and 9 at Month 12.

Reference	Study details	Main results
		During treatment, DQLI score decreased by 50% in the first 6 months; the TABQOL score decreased by 41% from Month 0 to 12. HADS score decreased by 50% from both Month 0 to 6, and Month 0 to 12. Adverse events were reported by 22 patients; most were infections (n = 21), none of which were severe or life-threatening. The one-year mortality rate was 0%.
Kanokrungsee et al. (2021)	53 patients with pemphigus treated with rituximab at a hospital in Thailand; in 45 patients rituximab was a second- or third-line treatment. Patients received either four weekly infusions of 375 mg/m^2 rituximab or 1,000 mg two weeks apart. 14 patients had PF.	11 of 14 patients with PF (78.6%) achieved complete remission (no new and/or established lesions for at least 2 months) on therapy over a median time of 5.28 months; 4 of 14 patients (28.6%) achieved complete remission off therapy. Four of 11 patients (36.4%) who achieved complete remission relapsed after a median duration of 20.2 months. Among the 53 patients treated with rituximab, adverse events were reported in 18 patients: infections were reported in 12 patients, 4 were severe requiring hospitalisation. No patients died during follow-up (8 months after treatment).
Palacios-Alvarez et al. (2021)	12 patients with PF: 11 received a first cycle of rituximab as four weekly infusions of 375 mg/m^2 rituximab and one received 1,000 mg, two weeks apart. Five patients had a second cycle of rituximab treatment.	After a first infusion of rituximab, 6 patients (50%) showed a complete remission off minimal therapy (defined as prednisolone [or equivalent] at ≤ 10 mg/day and/or minimal adjuvant therapy for at least 2 months) and 5 patients (42%) had partial remission on and off minimal therapy. Relapses occurred in 6 patients (50%) after a median of 12 months (range 7 to 55 months). Adverse events were reported in four patients; one experienced tuberculous meningitis but causality was not established.
BP: bullous pemphigoid; DQLI: Dermatology Quality of Life Index (lower scores show better outcomes); HADS: Hospital Anxiety and Depression Scale; iv: intravenous; MMP: mucous membrane pemphigoid; PF: pemphigus foliaceus; TABQOL: Treatment of Autoimmune Bullous Disease Quality of Life		