

Clinical Commissioning Policy: Rituximab for Immunobullous Disease

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Clinical Commissioning Policy: Rituximab for immunobullous disease

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**Prepared by NHS England Specialised Services Clinical Reference Group for
Specialised Dermatology**

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Policy Statement

NHS England will commission rituximab for immunobullous disease in accordance with the criteria outlined in this document. In creating this policy NHS England has reviewed this clinical condition and the options for its treatment. It has considered the place of this treatment in current clinical practice, whether scientific research has shown the treatment to be of benefit to patients, (including how any benefit is balanced against possible risks) and whether its use represents the best use of NHS resources. This policy document outlines the arrangements for funding of this treatment for the population in England.

Equality Statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

- Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and
- Given regard to the need to reduce inequalities between patients in access to, and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities

Plain Language Summary

About immunobullous diseases

Immunobullous diseases are a type of 'auto-immune' illness – this is where the body's immune system doesn't work properly. They can cause blistering and erosion (eating away of the surface) of the skin and mucous membranes of the mouth, eyes and genitals. The main immunobullous disorders are:

- **Pemphigus** – this causes blistering and erosions inside the mouth and on the skin. In some patients this can affect large areas of the body and may lead to death.

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- **Pemphigoid** (including linear IgA disease) – this causes blisters, intense itching and pain. Some forms of pemphigoid affect the eyes and can lead to blindness. In other patients the breathing tubes are affected which can lead the patient to sound hoarse and have difficulty breathing.
- **Epidermolysis bullosa acquisita (EBA)** – this is a less common illness that reduces the skin's ability to deal with friction. This causes blisters where the skin gets rubbed and may also affect the mouth, throat, stomach and gut.

Dermatitis herpetiformis is not included within this policy.

About current treatment

Currently there is no cure and patients may need treatment for many years. Treatments will usually include medicines that dampen down the body's immune response, such as steroids and immuno-suppressants.

About the new treatment

Rituximab belongs to a group of drugs known as 'monoclonal anti-bodies'. It is a biological medicine that works by 'targeting' specific proteins (receptors) on the surface of cells relevant to the cause of the disease. There is clinical interest in whether rituximab may be effectively used to treat patients with immunobullous diseases which are not controlled by conventional treatment.

What we have decided

NHS England has carefully reviewed the evidence to treat pemphigus and pemphigoid with rituximab. We have concluded that there is enough evidence to consider making the treatment available in adults and children who meet the defined criteria.

NHS England has also carefully reviewed the evidence to treat epidermolysis bullosa acquisita with rituximab. We have concluded that there is not enough evidence to make the treatment available at this time.

1 Introduction

This document describes the evidence that has been considered by NHS England to support a policy to routinely commission rituximab in the treatment of pemphigus and pemphigoid in adults and children who meet the defined clinical criteria; and a proposal to not routinely commission rituximab in the treatment of epidermolysis bullosa acquisita. This document also describes the criteria for commissioning, governance arrangements and funding mechanisms.

Immunobullous diseases are autoimmune disorders that result in blistering and erosion of the skin and mucous membranes. Autoimmune blistering diseases are characterised by the production of pathogenic auto-antibodies that are responsible for the formation of epidermal blisters. Immunobullous diseases are significantly life threatening and potentially fatal. Disease specific mortality estimates are 2-3 times higher compared with the general population.

The principal immunobullous disorders are pemphigus, pemphigoid (including linear IgA disease), epidermolysis bullosa acquisita (EBA), and dermatitis herpetiformis.

Pemphigus and its variants present with blistering and erosions inside the mouth, on the skin or in both locations. The diagnosis of pemphigus relies on clinical examination together with skin biopsy, direct immunofluorescence and serological testing. If treatment fails pemphigus can be fatal due to overwhelming systemic infection and fluid losses through the skin. In severe cases pemphigus can cause scarring and therefore good wound care is important to promote healing and prevent infection.

Initial treatment is the administration of oral corticosteroids in conjunction with “steroid sparing” immunosuppressants. Adjuvant immunosuppressants include drugs such as azathioprine, mycophenolate mofetil or cyclophosphamide. Whilst effective in many patients these medications can have significant systemic side effects and require careful monitoring.

Pemphigoid and its variants (including linear IgA disease) cause blisters, itching and pain; mucous membrane inflammation such as the aerodigestive tract and eyes can lead to life-threatening strictures and blinding ocular surface scarring. Pemphigoid can sometimes be treated with topical steroids though in many cases oral corticosteroids,

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alone or with other immunosuppressants, are required because of more severe, widespread or recalcitrant blistering. Good wound care is important to promote healing and prevent infection and scarring. Systemic steroids are not able to control progression in some variants of pemphigoid and dapsone, azathioprine, mycophenolate mofetil or cyclophosphamide are used in refractory cases.

Epidermolysis bullosa acquisita (EBA) is a less common immunobullous disease that causes blisters on the skin and can also affect the mouth, throat and digestive tract. Treatment pathways are similar to those used in pemphigus and pemphigoid.

Rituximab is an anti-CD20 chimeric monoclonal antibody that reduces circulating B cells numbers and prevents their maturation into antibody-secreting plasma cells. Rituximab is administered either as four infusions, each 375mg/m², given at weekly intervals infusions over 4 weeks (the "lymphoma protocol") or 2 infusions of 1g, two weeks apart (the "rheumatoid arthritis protocol") for the treatment of autoimmune diseases such as rheumatoid arthritis. As with all immunosuppressive therapy there is a risk of infection following infusion and appropriate patient selection and counselling is important prior to treatment.

Rituximab is licensed in adults to treat two forms of non-Hodgkin's lymphoma, chronic lymphocytic leukaemia, severe rheumatoid arthritis and two forms of severe vasculitis (EMA/614203/2010). It is not licensed for the management of the indications described in this policy.

2 Definitions

Immunobullous diseases are autoimmune disorders that result in the blistering of the skin. The principal immunobullous disorders are pemphigus, pemphigoid, epidermolysis bullosa acquisita (EBA), linear IgA disease and dermatitis herpetiformis.

Pemphigus and its variants present with blistering and erosions inside the mouth, on the skin or in both locations. Pemphigus results from the development of autoantibodies against adhesion proteins in the epidermis, notably desmogleins 1 and 3.

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Pemphigoid and its variants (including linear IgA disease) cause blisters, itching and pain, inflammation and scarring of mucosal membranes including the eyes and oesophagus. Pemphigoid results from the development of autoantibodies against various proteins in the epidermal basement membrane.

Epidermolysis bullosa acquisita (EBA) is a less common immunobullous disease that causes blisters on the skin and can also affect the mouth, throat and digestive tract. EBA results from the development of autoantibodies against type VII collagen.

Rituximab is an anti-CD20 chimeric monoclonal antibody. It reduces circulating B cells and prevents their maturation into antibody-secreting plasma cells.

3 Aims and Objectives

This policy aims to define NHS England's commissioning position on rituximab as part of the treatment pathway for adults and children with immunobullous diseases.

The objective is to ensure evidence based commissioning with the aim of improving outcomes for adults and children with immunobullous diseases.

4 Epidemiology and Needs Assessment

There are relatively few high quality studies in this area. The best data comes from the Langan et al., 2008(a) population based study. This study used a large general practice database and was rigorously controlled. Langan confirmed that, while pemphigus and pemphigoid can affect people of all ages, it is most common in older people. The median age at presentation of pemphigus patients was 71 years and pemphigoid patients was 80 years. There is a slight female predominance in each condition.

Pemphigus:

Langan (2008) found that the incidence of pemphigus was 0.7/100,000 patient years which gives a prevalence of 105 per million population in the UK.

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Pemphigoid:

The Langan et al., 2008 study found an incidence of pemphigoid of 4.3/100,000 patient years which correlates with expectations from clinical practice. This suggests that prevalence is in the order of 215 per million population in the UK. In the eyes the incidence is 0.8/1,000,000 population.

Epidermolysis bullosa acquisita:

There is no robust data on the epidemiology of this condition, though it is clearly less common than either pemphigoid or pemphigus (clinician consensus).

5 Evidence base

NHS England has concluded that there is sufficient evidence to support a policy for the routine commissioning of rituximab in the treatment of pemphigus and pemphigoid disease in adults and children who meet the defined clinical criteria. Whilst evidence is limited it is recognised that the rarity of the condition means that high quality level 1 evidence is unlikely to become available to support the commissioning position. NHS England has concluded that there is not sufficient evidence to support a policy for the routine commissioning of rituximab in the treatment of epidermolysis bullosa acquisita.

The clinical evidence review aimed to address the following research questions:

Question 1: Is rituximab clinically effective in the treatment of:

- a) Pemphigus and its variants (vulgaris, foliaceus, paraneoplastic, vegetans, IgA)?
- b) Pemphigoid and its variants (bullous pemphigoid, mucous membrane pemphigoid, linear IgA disease)?
- c) Epidermolysis bullosa acquisita?

Question 2: Is rituximab a safe drug to use in patients with the above indications?

Question 3: Is rituximab cost effective for use in patients with the above indications?

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In summary, for the cohort of refractory patients with pemphigus and pemphigoid there is a body of level 3 evidence derived from systematic reviews and phase two studies that consistently demonstrates both rapid onset ($\leq 1-3$ months) and high levels of clinical response. The evidence also demonstrates complete remission rates that range from $\geq 66\%$ to 75% and up to 80% , often in response to a single cycle. There is also evidence of adjuvant (steroid and immunosuppressive agent) treatment sparing effects. Relapse rates were of the order of $40-50\%$ with previously observed responses recurring on retreatment with rituximab. Times to relapse were typically in the order of $12-18$ months.

The evidence would support the “rheumatoid arthritis protocol” in terms of higher response rates and greater steroid sparing effect, however, it may also be associated with higher relapse rates.

More detailed findings are summarised below.

Question 1a: Is rituximab clinically effective in the treatment of pemphigus and its variants (vulgaris, foliaceus, paraneoplastic, vegetans, IgA)?

The main evidence for the use of rituximab in the management of pemphigus and its variants comes from three recently published systematic reviews – Wang et al., 2015, Ahmed et al., 2015 and Amber et al., 2015. These three reviews include the majority of the studies published on this topic and predominantly focus on the optimal rituximab regimen for treatment of pemphigus and its variants to achieve greatest clinical benefit.

Wang (2015) examined different rituximab regimens, the lymphoma protocol (LP) and the rheumatoid arthritis protocol (RA), for the treatment of pemphigus and its variants while Ahmed (2015) provided an analysis of treatment outcomes in patients with pemphigus vulgaris only. Amber (2015) reported on the clinical outcomes and relapse in 155 pemphigus patients treated with a single cycle of rituximab. There is, however, a lack of consistency in defining and reporting outcomes across these three reviews.

All three reviews found a positive clinical response to rituximab. Out of these, two (Wang et al., 2015 and Amber et al., 2015) found no difference in clinical outcomes between the RA and LP protocols for complete remission. Ahmed (2015) found patients in the

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RA protocol had a significantly better clinical response, with fewer numbers requiring corticosteroids or ISAs but had a non-significant higher rate of relapse.

Wang (2015) also reports on the immunoadsorption (IA) and rituximab combined protocol. When compared to higher dose and lower dose groups, the combined protocol group had the fastest control of disease before the completion of rituximab therapy. However, there was a trend for a higher rate of serious adverse events (IA combined vs. high-dose vs. low-dose rituximab: 8.5% vs. 2.8% vs. 1.9%; $p = 0.06$) in the IA combined group.

All three reviews include outcomes reported by doses of rituximab (higher dose vs. lower dose) and report significantly higher rate of achieving clinical remission in the higher dose groups compared to the low dose groups. However, patients in the higher dose group had significantly higher levels of relapse. Wang (2015) also reports a statistically significant positive relation between complete remission and a higher dose of rituximab and shorter disease duration. The potential link between severity of the disease and relapse rate which could explain some of the results was not addressed.

A case series by Kim et al., 2011 of 199 patients included 16 patients resistant to conventional therapy who were treated with rituximab. It found that the complete/partial remission rate for pemphigus vulgaris was 77% at 5 years and 94% at 10 years after initial diagnosis. The corresponding rate for pemphigus foliaceus was 87% at 5 years and 98% at 10 years after initial diagnosis.

In summary, the three systematic reviews indicate that, notwithstanding the significant heterogeneity in study design, methodology and patient cohorts, treatment with rituximab results in a shorter time to achieve complete remission or time to disease control, longer duration of complete remission and lower need for treatment with corticosteroids or other immunosuppressive agents (ISAs). Therefore, while the body of evidence is limited to retrospective case series and case reports it is strongly supportive of the clinical effectiveness of rituximab for pemphigus and its variants.

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Question 1b. Is rituximab clinically effective in the treatment of pemphigoid and its variants (bullous pemphigoid, mucous membrane pemphigoid, linear IgA disease)?

Mucous membrane pemphigoid (MMP):

The evidence for clinical effectiveness of rituximab for MMP comes from a small number of case series, case reports with small sample size and two systematic reviews by Taylor et al., 2015 and Shetty et al., 2012.

Taylor et al., 2015 is a review of clinical outcomes for different treatments for MMP from 2 case series comprising a total of 31 patients on rituximab. All patients were treated with concomitant corticosteroids and immunosuppressant drugs of varying combination and doses. The two case series are reported separately and results from the bigger case series by Le Roux-Villet et al., 2011 which contained 25 patients and showed: 68% (17/25) of patients achieved complete remission at 12 weeks after 1 cycle; 90% (9/10) ocular patients were clear of disease after a mean follow-up of 10 weeks; 40% (10/25) relapsed at a mean 4 months (range 1-16 months).

Similarly, the review by Shetty et al., 2012 included 28 MMP patients from 2 case series (n=22) and 5 case reports (n=6). All were treated with rituximab using the Lymphoma protocol. 71% (20/28) patients had a complete response, 3 had a partial response, 2 were non-responders, 1 had stabilisation of disease and 1 died. Of the 28 patients treated with rituximab, 27 simultaneously received concomitant therapy with immunosuppressive and anti-inflammatory agents. 15 of the 28 patients required a second cycle within the short follow-up period provided. Relapse occurred in 6 of the 12 patients (50%) who were reported to have complete response after the first cycle of rituximab. Both reviews are limited by the inclusion of retrospective case series and case reports with small sample sizes. There is a lack of use of standardised methods for measuring clinical outcomes and the studies are confounded by concomitant use of other immunosuppressive drugs.

Overall there is a low level but supportive evidence for the use of rituximab for MMP.

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Bullous pemphigoid:

The evidence for the effectiveness for rituximab comes from a small number of case series, case reports with small sample size and one systematic review (Shetty et al., 2013). This review included the majority of the studies identified in the literature search.

The review by Shetty et al., 2013 included 1 case series with 5 patients and 8 case reports with 11 patients, of which 4 were children. 14 patients were treated with the Lymphoma Protocol and 2 patients according to the Rheumatoid Arthritis protocol. At 15.6 months 69% (11/16) of all patients achieved complete response, 6% (1/16) achieved partial response and 6 % (1/16) had no response. 19% (3/15) had died.

Recognising the limitations due to rarity and the small number of cases there is a low level but supportive evidence for use of rituximab in bullous pemphigoid cases.

Question 1c. Is rituximab clinically effective in the treatment of and epidermolysis bullosa acquisita?

No studies with a reasonable sample size were available from the literature search to generate evidence. The majority of the evidence is reported as case reports with limited information to formulate a conclusion.

Question 2: Is rituximab a safe drug to use in patients with the above indications?

Pemphigus:

Rituximab infusion-associated cytokine-release reactions such as fever, rigors, flushing, and chills are more common during initial infusions. Serious adverse events (SAE) associated with rituximab treatment include sepsis due to bacterial and viral infection, pulmonary embolism, neutropenia and deep venous thrombosis. Infusion related SAEs range from 2.8% in high dose group, 4.3% in LP group and 1.9% RA group. The IA-linked protocol was reported to result in higher SAEs at 8.5% (Wang et al., 2015). Ahmed et al., 2015 reported SAEs in 5% (9/184) of patients with 3 deaths in lymphoma protocol series 2% (4/209). The RA protocol resulted in 4 SAEs (n=209) with 2 deaths.

Another phase II study of rituximab in 45 patients with unresponsive pemphigus vulgaris found that over a follow-up period of 4.5 years, 22.5% of patients experienced

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complications including disseminated herpes, lung abscess, skin abscess, pneumonia, sepsis, and sinus cavernous thrombosis (Kamran et al., 2013).

Mucous membrane pemphigoid:

Shetty (2013), in a literature review of rituximab in mucous membrane pemphigoid, observed that in a case series of 20 patients, 2 patients developed serious infection, one developed pyelonephritis and the second died from complications of tuberculosis. Both patients had hypogammaglobinaemia at the time of infection. There were no adverse effects reported from another case series of 5 patients and 5 case reports consisting of 6 patients included in the review.

Bullous pemphigoid:

Shetty et al., 2013 reported that 3 out of 16 patients developed serious infections (clostridium difficile associated enteropathy, bacterial sepsis, varicella-zoster sepsis) of whom 2 died. Another patient died of cardiac complications 10 days after rituximab treatment.

In summary, while rituximab is not without risk, particularly in relation to infection, this must be considered in the broader context of recognising the adverse effects associated with comparator treatments, which include high dose steroids, azathioprine and cyclophosphamide.

Question 3: Is rituximab cost effective for use in patients with the above indications?

There was a lack of relevant cost effective studies. Heelam et al., 2015 provided a view on the healthcare cost impact of adding rituximab in the treatment regime in Canadian setting in 2013 based on healthcare utilisation data from 89 patients receiving rituximab for pemphigoid and pemphigus disorders. The majority (84%) of patients were in pemphigus vulgaris subgroup.

The results show that there was 30.3% decrease in direct healthcare costs (admissions, outpatient and home visits, investigations etc.) with the introduction of rituximab infusion in the treatment regime at a median duration of 28 months (1-256 months) from the time of biopsy diagnosis. The 6 month pre-rituximab costs was \$3.8 million and in the 6

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months post-rituximab it was \$2.6 million. The cost per patient was \$42,000 in the 6 months pre-rituximab and \$29,000 in the 6 months post-rituximab. Intravenous immunoglobulins (IVIG) was reported as the main cost driver representing 96% of the overall cost prior to rituximab infusion and 63% of the cost following rituximab administration.

The costing analysis did not include information on number of important factors including calculation of adverse events secondary to standard treatment versus rituximab. The costs of prophylactic medications in conjunction with corticosteroids (e.g., proton pump inhibitors, bisphosphonates) are not included in this analysis.

6 Criteria for Commissioning

Rituximab should be considered in treatment of pemphigus and pemphigoid disease in adults and children as a third or fourth line treatment option when other treatments, including systemic steroids and steroid sparing agents have failed to control the disease (see patient pathway for full details). The decision to treat using rituximab should be made by the specialist multi-disciplinary team and the patient, taking full account of the risk profile and contra-indications. This is particularly relevant when considering the use of rituximab in frailer elderly patients and its side effects profile.

Appropriate therapeutic endpoints to evaluate response in autoimmune immunobullous diseases would be shorter time to complete remission; achievement of complete remission off therapy and complete remission on therapy, both definitions applying to patients without lesions for at least 2 months and long duration of effect.

7 Patient Pathway

Once a diagnosis of an immunobullous disorder has been made, generally on the basis of clinical suspicion, characteristic biopsy findings and immunopathology either on serum (indirect immunofluorescence and relevant ELISAs) or on tissue (direct immunofluorescence) treatment should begin. The main objective will be to achieve clinical remission, control the disease, prevent relapses, and avoid adverse events normally associated with the prolonged use of steroids and immunosuppressive agents.

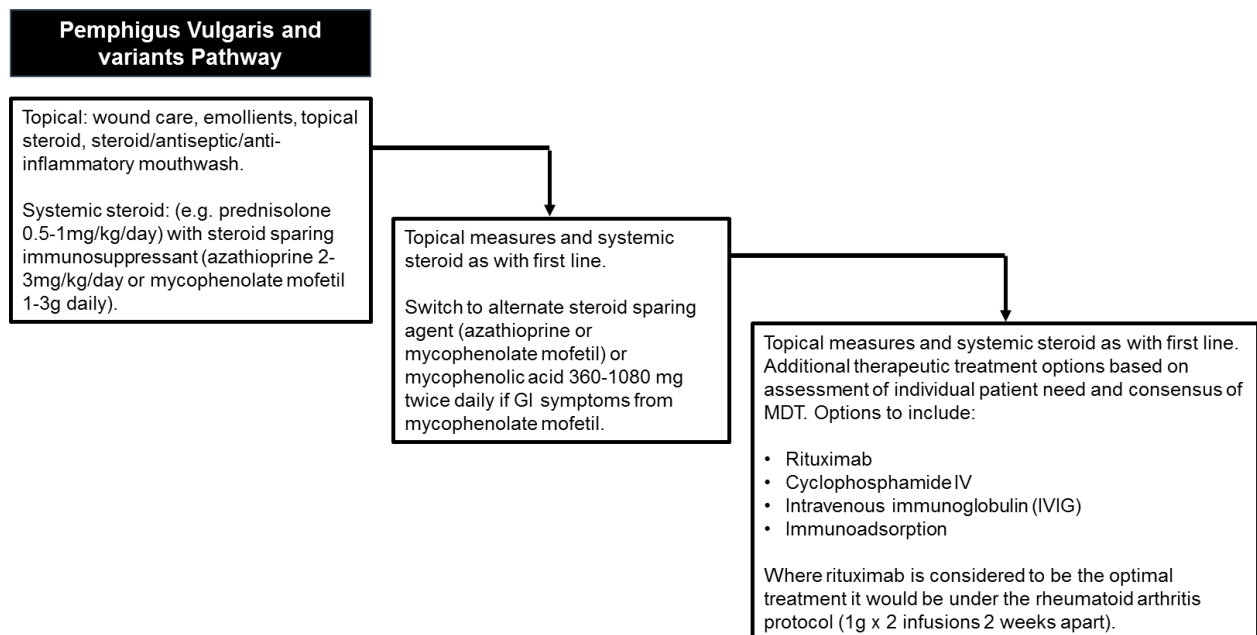
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There are many similarities in the management of the various immunobullous disorders, particularly in severe or refractory disease. There are however some differences in their initial management as outlined in the patient pathways below.

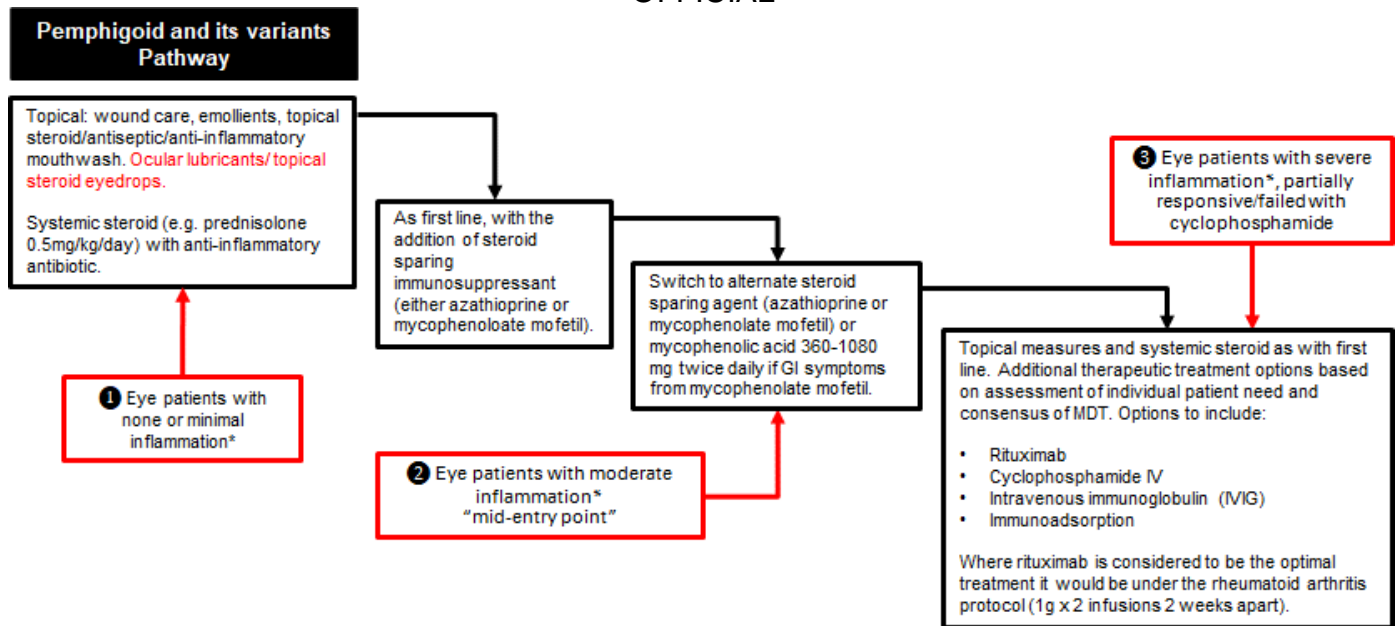
Based on expert clinical consensus it is estimated that 1% of patients with pemphigus require third line treatment. Approximately 1% of pemphigoid patients require fourth line treatment.

Rituximab should be considered as third line treatment in pemphigus and fourth line in pemphigoid. There is significant experiential evidence and as yet unpublished UK cost data, that indicates that rituximab is more effective and safer than cyclophosphamide and more cost effective and more convenient (and more rapidly effective) than IVIG.

Benefit from a single cycle of rituximab may last 9-18 months or more. Retreatment may be considered in the case of relapse.



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Footnotes

† Ocular mucous membrane pemphigoid is blinding in 20% of patients.

* Inflammation graded with the "Bulbar Conjunctival Hyperaemia Inflammation Scales" from Ong HS, et al Validation of a clinical assessment tool for cicatrising conjunctivitis. The Ocular Surface. 2020 Jan; 18(1):121-129.

8 Governance Arrangements

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.

9 Mechanism for Funding

Funding for rituximab in the treatment of immunobullous diseases in adults and children would be through the local NHS England specialised commissioning teams.

10 Audit Requirements

Specialist centres will be required to collaborate in an audit network and participate in an annual audit which will report on the following outcomes, collected following the administration of a course of two injections:

- Time to clinical remission, defined by healing of >75% of cutaneous / mucosal erosions
- Times to clinical, immunological and haematological relapse

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- Timing of and necessity for re-treatment
- Reduction/discontinuation in steroid and adjuvant immunosuppressant doses at 6 months post treatment
- Incidence of serious adverse effects

Specialist centres should also collaborate in national or international trials of new and existing therapies in patients with immunobullous disease. Such data should be published in the peer-reviewed literature. With respect to the role of Rituximab, research topics may include:

- The impact of adjuvant therapy on time to relapse
- Identification of clinical, immunological and genetic factors predictive of good/poor response to rituximab.

11 Documents which have informed this Policy

None.

12 Date of Review

This document will be reviewed when information is received which indicates that the policy requires revision. If a review is needed due to a new evidence base then a new Preliminary Policy Proposal needs to be submitted by contacting england.CET@nhs.net.

Our policies provide access on the basis that the prices of therapies will be at or below the prices and commercial terms submitted for consideration at the time evaluated. NHS England reserves the right to review policies where the supplier of an intervention is no longer willing to supply the treatment to the NHS at or below this price and to review policies where the supplier is unable or unwilling to match price reductions in alternative therapies.

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Appendix A

Change form for published Specifications and Products developed by Clinical Reference Group (CRGs)

Product name: Clinical Commissioning Policy: Ritiximab for Immunobullous Disease

Publication number: 16035/P

Description of changes required

The clinical commissioning policy: rituximab for immunobullous disease was published in 2016 following development by the CRG for Specialised Dermatology. Whilst the policy includes reference to ocular presentations of this disease, it is recommended that a few areas of the text are expanded as outlined below to clarify the pathway for patients presenting with single organ ocular disease. It is estimated that up to 20 patients annually may benefit from earlier access to effective treatment following this revision.

Describe what was stated in original document	Describe new text in the document	Section/Paragraph to which changes apply	Describe why document change required	Changes made by	Date change made
Pemphigoid and its variants (including linear IgA disease) cause blisters, itching and pain.	Pemphigoid and its variants (including linear IgA disease) cause blisters, itching and pain; mucous membrane inflammation such as the aerodigestive tract and eyes can lead to life-threatening strictures and blinding ocular surface scarring.	p.6/7 Introduction	Some forms of pemphigoid affect the eyes and can lead to blindness as stated on p5 ' About immunobullous diseases ' and p.14 ' Evidence Review ' The proposed additional wording expands the text to include impact of this disease on the eyes.	Clinical Representative, Specialised Ear and Ophthalmology CRG.	April 2021
Pemphigoid and its variants (including linear IgA disease)	Pemphigoid and its variants (including linear IgA disease)	P.8 Definition	Some forms of pemphigoid affect the eyes and can lead to	Clinical Representative, Specialised Ear and	April 2021

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<p>cause blisters, itching and pain. Pemphigoid results from the development of autoantibodies against various proteins in the epidermal basement membrane.</p>	<p>cause blisters, itching and pain, inflammation and scarring of mucosal membranes including the eyes and oesophagus. Pemphigoid results from the development of autoantibodies against various proteins in the epidermal basement membrane.</p>		<p>blindness as stated on p5 'About immunobullous diseases' and p.14 'Evidence Review'. The proposed additional wording adds 'inflammation of the eyes' to the more detailed definition.</p>	<p>Ophthalmology CRG.</p>	
<p>The Langan et al., 2008 study found an incidence of pemphigoid of 4.3/100,000 patient years which correlates with expectations from clinical practice. This suggests that prevalence is in the order of 215 per million population in the UK.</p>	<p>The Langan et al., 2008 study found an incidence of pemphigoid of 4.3/100,000 patient years which correlates with expectations from clinical practice. This suggests that prevalence is in the order of 215 per million population in the UK. In the eyes the incidence is</p>	<p>p.9 Epidemiology</p>	<p>Incidence of the disease specifically affecting the eyes has been added.</p>	<p>Clinical Representative, Specialised Ear and Ophthalmology CRG.</p>	<p>April 2021</p>

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	0.8/1,000,000 population.				
Treatment Pathway diagram	Treatment Pathway diagram add ocular lubricants to the first line care pathway and edit flowchart to reflect ocular presentations.	p.17 Treatment Pathway	Inclusion of specific ocular treatments	Clinical Representative, Specialised Ear and Ophthalmology CRG.	April 2021