NHS England

Evidence Review:

Rituximab for Immunobullous Disease

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1. Introduction

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. Pemphigoid can sometimes be treated with topical steroids though in many cases oral corticosteroids, 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.

2. Summary of results

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?

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 (≤1-3 months) and high levels of clinical response. The evidence also demonstrates complete remission rates that

range from ≥ 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 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.

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 al., 2013 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.

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 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 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.

3. Research questions

Is rituximab clinically effective in the treatment of pemphigus and its variants (vulgaris, foliaceus, paraneoplastic, vegetans, IgA), pemphigoid and its variants (bullous pemphigoid, mucous membrane pemphigoid, linear IgA disease) and epidermolysis bullosa acquisita?

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

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

4. Methodology

A review of published, peer reviewed literature has been undertaken based on the research questions set out in Section 3 and a search strategy agreed with the lead clinician and public health lead for this policy area. This has involved a PubMed search and search of the Cochrane database for systematic reviews, in addition to review of any existing NICE or SIGN guidance. The evidence review has been independently quality assured.

An audit trail has been maintained of papers excluded from the review on the basis of the inclusion and exclusion criteria agreed within the search strategy. The full list has been made available to the clinicians developing the policy where requested.

5. Results

A detailed breakdown of the evidence is included in the Appendix.

Appendix One

Level	Study design and intervention			Outcomes					Reference	Other		
Level of evidence	Study design	Study size	Intervention	Category	Primary Outcome	Primary Result	Secondary Outcome	Secondary Result	Reference	Complications noted	Benefits noted	Comments
3	Systematic	Only rituximab related studies. A total 31 patients for two case series (25 Le Roux-Ville et al., 2011 and 6 patients in Lourari et al., 2011) The authors have not included detailed case reports.	Combination of rituximab and immunosuppressants (dapsone, sulfasalazine or both).	Clinical effectiveness of the intervention	Regression of healing of mucosal lesions classed as responders (complete response or partial response) and non-responders.	Le Roux-Villet et al., 2011 - A series of 25 mucous membrane pemphigoid (MMP) (10 with ocular disease) patients treated with 1 - 2 cycles rituximab and adjuvants, including dapsone and/or sulfasalazine and topical corticosteroids. 17 of 25 in complete remission at 12 weeks after 1 cycle; 9 of 10 ocular patients were clear of disease after mean of 10 weeks. 10 of 25 relapse at mean of 4 (range 1-16) months. 2 of 25 died (also on immunosuppressant medications). Lourari et al., 2011 - A series of 6 MMP patients treated with rituximab with unspecified adjuvant immunosuppressants - 4 out of 6 experienced complete remission on therapy.	None	NA	Taylor, J.; McMillan, R.; Shephard, M.; Setterfield, J.; Ahmed, R.; Carrozzo, M.; Grando, S.; Mignogna, M.; Kuten-Shorrer, M.; Musbah, T.; Elia, A.; McGowan, R.; Kerr, A. R.; Greenberg, M. S.; Hodgson, T.; Sirois, D.. World Workshop on Oral Medicine VI: a systematic review of the treatment of mucous membrane pemphigoid. Oral Surg Oral Med Oral Pathol Oral Radiol 2015;120(2):161-171.e20.	Not available	As per primary outcome measure	Population: Age information not given. Indication is mucous membrane pemphigoid (MMP) with a subgroup of ocular MMP. Summary comments: This is a systematic review of all treatments used in the management of mucous membrane pemphigoid (MMP) with a subgroup of ocular MMP presented with good description objective, study search and selection methods, inclusion and exclusion criteria, methodological assessment and data synthesis with statistical methods for analysis. The review doesn't include pooling of outcome results and meta analysis. For rituximab only 4 studies (two case series by Le Roux-Villet et al., 2011 and Lourari et al., 2011) and 2 case reports by Taverna et al., 2007; Schmidt et al., 2009) met study criteria. The authors do not report on 2 case reports. For the case series Le Roux-Ville et al., 2011, with 25 patients, the authors report that after 1 - 2 cycles of rituximab and adjuvants, including dapsone and/or sulfasalazine and topical corticosteroids - 17 of 25 patients were in complete remission at 12 weeks after 1 cycle; 9 of 10 ocular patients were clear of disease after a mean of 10 weeks. There is no more information available on patient selection, baseline characteristics, or the definition of primary outcome etc. Hence, level 3 rating of evidence specific to MMP.

3	Systematic + Meta Analysis	578 patients with pemphigus	Rituximab	Clinical effectiveness of the intervention	Complete remission (CR) rate after the first cycle of rituximab, time to disease control (TDC), time to CR on or off therapy (total complete remission (TCR) on or TCR off), duration of CR and relapse rate.	For all studies combined, CR was achieved in 76% of patients with a mean TDC of less than one month, and mean TCR of 5.8 months after a cycle of rituximab. Mean remission duration was 14.5 months, with an overall relapse rate of 40%. 38.7% were off all therapies, with mean CR off of 15.1 months after a cycle of rituximab. In a study of patients treated primarily with conventional therapy (corticosteroids plus immunosuppressants), 77% attained CR, and 51% were off all therapy with a 6-year mean follow-up. The mean TCR off was 36 months using conventional therapy. The overall rate of CR using rituximab was similar to conventional therapy, but the time to CR off all therapies was shorter for patients treated with rituximab, even in refractory or severe cases. High dose rituximab treatment was associated with significantly longer duration of CR and a trend for shorter TDC and lower relapse rate compared with low-dose rituximab treatment. The rates of serious adverse events were similar between the 2 groups. However, in the two comparator studies included in this review (Kanwar et al., 2014 and Cho et al., 2014) observed no significant difference in outcomes between patients treated with high-dose and low-dose rituximab. The authors report that disease severity must be taken into account when evaluating the efficacy of rituximab. Both high-dose and low-dose rituximab could eventually lead to CR, but more sustained CR might be reached using higher dose rituximab. The IA-combined protocol resulted in 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. The lymphoma protocol was linked to a trend towards higher CR, shorter TDC and TCR on, and longer remission duration, although the difference was not clinically significant . However, the lymphoma protocol had higher total dose of the compared with the rheumatoid arthritis (RA) protocol.	NA	NA	Wang, Hsiao-Han; Liu, Che-Wei; Li, Yu-Chuan; Huang, Yu-Chen. Efficacy of Rituximab for Pemphigus: A Systematic Review and Meta-analysis of Different Regimens. Acta Derm. Venereol. 2015;0(0):0.	Two patients experienced serious infections. One developed severe pyelonephritis and the second died from a complication of tuberculosis.	NA	Population: Age information not given. Indication is both pemphigus vulgaris and pemphigus foliaceus. Summary comments: This is a systematic review and meta analysis of studies of the evaluation of rituximab in the management of pemphigus vulgaris and pemphigus foliaceus. The review includes a good description of the objective, study search and selection methods, inclusion and exclusion criteria, methodological assessment, and data synthesis with statistical methods for analysis. Key limitation is the inclusion of retrospective case series with differing definitions of inclusion criteria, patient selection methods, and heterogeneity. All patients were on treatment with other immunosuppressive drugs and the impact of drugs these on the outcomes cant be ruled out.
3	Systematic	16	Rituximab based lymphoma protocol - once weekly infusions at dose of 375mg/m2 per infusion as single cycles.	Clinical effectiveness of the intervention	Complete response - absence of new lesions and healing of previous lesions while on or off systemic therapy. Partial response - healing loss of less than 50% of present prior to initiating rituximab or occurrence of transient new lesions while on systemic therapy. No Response - no change in the clinical profile despite use of rituximab and concomitant therapy.	14 out of 16 were treated with the Lymphoma Protocol and 2 patients according to the Rheumatoid Arthritis Protocol. After a mean follow-up of 15.6 months 11/16 (69%) had a complete response, 1 (6%) partial response, 1 (6%) no response and 3 (19%) patients died. 38% of the patients required more than one dose of rituximab.	None	NA	Shetty, Shawn; Ahmed, A. Razzaque. Treatment of bullous pemphigoid with rituximab: critical analysis of the current literature. J Drugs Dermatol 2013;12(6):672-677.	3 deaths	As per primary outcome	Population: Age range of 6 to 66 years. Indication is bullous pemphigoid. Summary comments: This is a systematic review of patients with bullous pemphigoid treated with rituximab. The study has a objective with inclusion criteria but has a poor description of search methodology, study quality assessment and statistical methods to pool the data. The review identified 1 case series with 5 patients and 8 case report with 11 patients. Rituximab resulted in complete response in 69% of patients and 3 died. The study is seriously limited due to inclusion of small number of patients from case series and case reports and poor methodology. It is difficult to generalise the findings of the study.

3	Systematic	28	Rituximab using the lymphoma protocol, which involves a dose of 375 mg/m2 administered weekly for 4 consecutive weeks.	Clinical effectiveness of the intervention	Complete response, partial response, stabilisation of disease and no response.	20 of 28 patients had complete remission (CR), 3 had a partial response (PR), 2 were no response (NR), 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. Relapses occurred in 6 of the 12 patients (50%), who were reported to have CR after the first cycle of rituximab; they occurred after a mean follow-up of 9.8 months.	None	NA	Shetty, Shawn; Ahmed, A. Razzaque. Critical analysis of the use of rituximab in mucous membrane pemphigoid: a review of the literature. J. Am. Acad. Dermatol. 2013;68(3):499-506.	NA	As per primary outcome.	Population: Age information not given. Indication is refractory mucous membrane pemphigoid. Summary comments: This is a systematic review of patients with mucous membrane pemphigoid treated with rituximab by the Lymphoma Protocol. It included 28 patients from 2 case series and 5 case reports. The study has an objective with inclusion criteria but has poor description of search methodology, study quality assessment and statistical methods to pool the data. The results are by the 2 case series identified in the search but the number of patients included doesn't match the number of patients described in the methodology. The results show that 20/28 patients had a complete response and nearly all of them were treated with concomitant treatment. A relapse rate was reported only for patients who had complete response after the first dose and was 50%. Overall the generalisability of the study are limited due to the inclusion of small number of case series and case reports with reporting of results.
0	Other	89 patients	Rituximab	Clinical effectiveness of the intervention	To compare health system resource use and associated costs in patients with auto immune bullous diseases for a 6-month period prior to and for 6 months following commencement of the first rituximab therapy.	The overall cohort cost for the entire cohort in the 6 months pre-rituximab was $3.8 million and in the 6 months post-rituximab was $2.6 million (30.3% decrease). The main cost driver for the entire cohort was IVIG, representing 96% of the overall cost prior to rituximab infusion and 63% of the cost following rituximab administration. The cost per patient was $42,000 in the 6 months pre-rituximab and $29,000 in the 6 months post-rituximab.	None	NA	Heelan, Kara; Hassan, Shazia; Bannon, Grace; Knowles, Sandra; Walsh, Scott; Shear, Neil H.; Mittmann, Nicole. Cost and Resource Use of Pemphigus and Pemphigoid Disorders Pre- and Post-Rituximab. J Cutan Med Surg 2015;19(3):274-282.	Costs of complication included	NA	Population: Patients had a mean age of 48 years. Indication is both pemphigoid and pemphigus. Summary comments: For full summary of study please see summary of results in the Evidence Review under question 3: is rituximab cost-effective?

3	Case series	21 patients	Cohort 1 - 3 patients with multiple treatments. Cohort 2 - 13 patients started with sequential steroid sparing agent with azathioprine, mycophenolate mofetil (MMF) and rituximab. Cohort 3 - started with MMF without steroids.	Clinical effectiveness of the intervention	1. Disease 'remission' defined as disease control for at least 2 years off all immunosuppressive drugs. 2. Disease 'control' defined as having no skin or mucosal disease activity and being off steroids for at least 3 months, while continuing on an oral immunosuppressive agent, or being within 2 years of a rituximab dose.	Rituximab related primary outcome measures. 13 patients who failed therapy with MMF subsequently received rituximab. All 13 patients showed a major response to the first course, with 11 controlled off steroids; one achieved complete remission. Seven patients who could be followed up were initially controlled, but relapsed within 2 years of observation. All seven responded to a second course of rituximab, with three subsequently relapsing, again responding to a third course. Patients were controlled for a significantly longer period after rituximab than azathioprine (P = 0.015), but for a similar time to MMF (P = 0.059), with a mean time to failure of 364 days. Response to the second rituximab course was similar to the first (P = NS). Rituximab was well tolerated, the only significant side-effect observed being a post-infusion febrile reaction in a single patient, without evidence of systemic sepsis; symptoms spontaneously settled over 2 weeks. Rituximab had a superior steroid-sparing effect compared with azathioprine and mycophenolate. The median daily average prednisolone dose during azathioprine therapy was 18 mg, compared with 16 mg for MMF (P = 0.028 vs azathioprine) and 5.6 mg after the first course of rituximab (P = 0.008 vs azathioprine, P =0.012 vs MMF). The steroid-sparing effect of rituximab appeared even stronger on subsequent courses, corresponding values falling to 2.5 mg/d and 3 mg/d after the second and third courses respectively (P = 0.018 for the comparison between courses one and two;). Finally, the proportion of patients achieving a mean daily prednisolone dose below 10 mg/d was 0% (0/11) for azathioprine, 29% (5/17) for mycophenolate (P = NS) and 62% (8/13) after the first course of rituximab (P = 0.016 vs azathioprine; P = 0.031 vs MMF).	None	NA	Ojaimi, S.; O'Connor, K.; Lin, M. W.; Schifter, M.; Fulcher, D. A.. Treatment outcomes in a cohort of patients with mucosal-predominant pemphigus vulgaris. Intern Med J 2015;45(3):284-292.	As per primary outcome measures	As per primary outcome measures	Population: Mean age of 53.4 years. Indication is pemphigus vulgaris. Summary comments: This small prospective study of 21 patients with Pemphigus vulgaris (PV). 13/21 who were not controlled with subsequent treatment with steroids, azathioprine and mycophenolate received rituximab. The generalisability of this study is limited by the small number and confounding due to background treatment with other anti-PV drugs.

3	Case series	45 patients with pemphigus vulgaris (PV) who received rituximab, four doses of 375 mg/m2 intravenously weekly, plus concomitant oral prednisolone.	Rituximab, four doses of 375 mg/m2 intravenously weekly, plus concomitant oral prednisolone.	Clinical effectiveness of the intervention	Rate of initial and marked clinical improvement and marked clinical improvement. Initial clinical improvement was defined as the time from the first rituximab infusion to cessation of new blister formation, negative Nikolsky sign and re-epithelialization of the earlier lesions. Marked clinical improvement was defined as the above defined clinical improvement parallel to prednisolone dose reduction. Relapse was defined as the clinical disease progression (new blister or positive Nikolsky sign) and an inevitable increase in the dose of prednisolone for disease control after a clinical improvement.	40 out of 45 patients completed the study. Following treatment with rituximab, all the analysed patients with PV had initial clinical improvement after a mean period of 6.35 weeks and a marked clinical improvement after a mean of 10.13 months. Following an initial clinical improvement, 21 out of 40 patients (52.5%) had a relapse after a mean period of 7.98 ± 6.02 months, with 9 defined as major and 12 defined as minor relapse.	1.Prednisolone doses (mg/d) at baseline, three months, six months and the last visit. 2. Side effects of Rituximab.	1. The mean prednisolone dose (mg/d) decreased significantly from a baseline level of 48.75 ± 25.86 to 26.50 ± 12.95 at three months, 20.70 ± 17.51 at six months, and 15.26 ± 9.98 at the last visit (P = 0.0001). 2. The side-effects following rituximab were reported as Lung abscess (n=1), sepsis (n=1), pneumonia (3), cavernous sinus thrombosis (n=2), skin abscess (n=1), deep vein thrombosis (n=3), generalized arthralgia (n=1), and Stevens–Johnson syndrome (n=1)	Balighi, Kamran; Kamran, Balighi; Daneshpazhooh, Maryam; Maryam, Daneshpazhooh; Khezri, Somayeh; Somayeh, Khezri; Mahdavi-nia, Mostafa; Mostafa, Mahdavi-nia; Hajiseyed-javadi, Mahsa; Mahsa, Hajiseyed-javadi; Chams-Davatchi, Cheyda; Cheyda, Chams-Davatchi. Adjuvant rituximab in the treatment of pemphigus vulgaris: a phase II clinical trial. Int. J. Dermatol. 2013;52(7):862-867.	Refer outcomes	refer outcomes	Population: Mean age 40.5 years. Indication is refractory pemphigus vulgaris (PV). Summary comments: A medium sized prospective case series of 45 patients with refractory PV. The findings are limited by potential for bias due to a lack of comparator, and an open label treatment with un-blinded assessment of clinical response. The definition of the response varied from established international standards. As all patients received background steroids and nearly 50% who relapsed subsequently received other treatment the confounding effect of these treatment can not be ruled out.
3	Case series	113 patients (rituximab - 22 patients)	Adjuvant treatment with - Azathioprine (AZ), cyclophosphamide (CY), mycophenolate mofetil (MM); rituximab (RTX), or traditional adjuvant (TA) (including AZ & MM & CY).	Other	Patients assessed quality of life (QoL) – measured using the SF-36 questionnaire (a general health status indicator), Skindex-29 (a dermatology-specific QOL instrument), and the 12-item General Health Questionnaire (GHQ) (to detect the possible presence of nonpsychotic psychiatric disorders, e.g. depression and anxiety). Answers were given on a 4-point scale and scored as 0-0-1-1. Patients scoring ‡ 4 on the GHQ were defined as ‘GHQ-12-positive cases’ (GHQ+).	There were no significant differences between the treatment subgroups for either questionnaire. However, the MM and rituximab subgroups had better scores for the SF-36 physical component summary (PCS) scores, and the rituximab subgroup had the worst score on the symptom scale of the Skindex-29 indicating higher severity of comorbidity when starting treatment. NAT patients had lower scores on most of the SF-36 scales, with significant differences compared with patients receiving rituximab for the components role-physical (P = 0.02), vitality (VT) (P = 0.01) and mental health (MH) (P = 0.01).	None reported	NA	Paradisi, A.; Cianchini, G.; Lupi, F.; Di Pietro, C.; Sampogna, F.; Didona, B.; Pagliarello, C.; Tabolli, S.; Abeni, D.. Quality of life in patients with pemphigus receiving adjuvant therapy. Clin. Exp. Dermatol. 2012;37(6):626-630.	As per primary outcome measure	As per primary outcome measure	Population: Mean age of 50 years. 103 patients with pemphigus vulgaris and 10 patients with pemphigus vulgaris. Summary comments: A prospective study of 113 patients who had pemphigus vulgaris (n=103) or pemphigus foliaceus (n=10) assessed for QoL using validated tools. The patients were grouped by adjuvant treatment received compared against patients not receiving any adjuvant treatment. The main limitations of the study include the lack of details of blinding in both the assessor and patients which could bias the results. As all patients were receiving prednisolone the impact of this treatment can not be objectively estimated and there is no information relating how quality of life (QoL) was related to response to treatment.

3	Case series	23 (this study is included in the systematic review by Wang et al 2015)	immunoadsorption (IA) and dexamethasone and rituximab and azathioprine and mycophenolate (IA was administered on days 1, 2, 3 (first treatment cycle), 21, 22 and 23 (second treatment cycle), while dexamethasone pulses (100 mg intravenously) were given on days 2, 3, 4 (first treatment cycle), 22, 23 and 24 (second treatment cycle). Rituximab (Mabthera ; Roche, Basle, Switzerland) was infused at a dose of 1000 mg on days 4 and 24 (one treatment cycle). In addition, all patients received azathioprine (at a dose adjusted to the activity of thiopurine-S-methyltransferase) or, in case of side-effects of azathioprine, mycophenolate mofetil (2000 mg daily).	Clinical effectiveness of the intervention	Circulating antibodies, clinical outcomes, partial remission on therapy, complete remission on therapy and complete remission off therapy	All patients showed decline of circulating auto-antibody levels with improvement of pemphigus lesions within the first weeks of therapy and long-term complete remission was induced in 19 (83%) patients. In the remaining four patients, one (4%) had minimal disease and in three (13%) partial remissions were observed. Over the long-term follow-up of 11-43 (mean 29) months, six (26%) patients had a recurrence and in two (9%) patients, severe adverse events occurred.	None	NA	Kasperkiewicz, M.; Shimanovich, I.; Meier, M.; Schumacher, N.; Westermann, L.; Kramer, J.; Zillikens, D.; Schmidt, E.. Treatment of severe pemphigus with a combination of immunoadsorption, rituximab, pulsed dexamethasone and azathioprine/mycophenolate mofetil: a pilot study of 23 patients. Br. J. Dermatol. 2012;166(1):154-160.	2 incidences - 1 sepsis, 1 paraplegia	As per primary outcome measure	Population: Mean age of 55 years. 17 patients with pemphigus vulgaris and 6 patients with pemphigus foliaceus. Summary comments: This is a prospective study of 23 patients with pemphigus treated with combined immunoadsorption and dexamethasone and rituximab and azathioprine and mycophenolate. Complete remission was induced in 19 (83%) patients. In the remaining four patients, one (4%) had minimal disease and in three (13%) partial remissions were observed. Over the long-term follow-up of 11-43 (mean 29) months, six (26%) patients had a recurrence and in two (9%) patients, severe adverse events occurred. The study is limited by the small sample size and patient selection criteria. All patient received varying combination of other immunosuppressive drugs. The generalisability of results is limited because of above limitations.
3	Case series	199 patients diagnosed with pemphigus vulgaris (PV) and pemphigus foliaceus (PF)	16 patients recalcitrant to conventional therapy were treated with rituximab.	Clinical effectiveness of the intervention	Complete remission, partial remission	Complete/partial remission rate for PV was 77% at 5 years and 94% at 10 years after initial diagnosis. The corresponding rate for PF was 87% at 5 years and 98% at 10 years after initial diagnosis. There was no difference in time to remission between mild cases (treated with prednisolone (Pd) alone) and severe cases (treated with Pd ± adjuvant therapy).	None	NA	Kim, Mi Ri; Kim, Hyeon Chang; Kim, Soo-Chan. Long-term prognosis of pemphigus in Korea: retrospective analysis of 199 patients. Dermatology (Basel) 2011;223(2):182-188.	None mentioned in the abstract	As per primary outcome measure	Population: Mean age 46.1 years. Indication is both pemphigus vulgaris and pemphigus foliaceus. Summary comments: This is retrospective study of 199 patients with PV or PF identified between 1993 and 2008. The case series included sixteen patients who were resistant to conventional therapy and received rituximab. Authors report all 16 patients achieved overall remission and no additional findings reported in the abstract. Full article was not studied because of the small number of patients and this study is included in the meta analysis by Wang et al., 2015 which is included in the evidence review.

3	Systematic	155 patients - 124 with pemphigus vulgaris (PV) and 31 with pemphigus foliaceus (PF)	Rituximab - Rheumatoid Arthritis (RA) protocol (1000 mg weekly * 2 weeks). Low-dose RA protocol (500 mg weekly * 2 weeks). Lymphoma protocol (375 mg/m2 * 4 weeks). Low-dose lymphoma protocol (375 mg/m2 * 2 weeks).	Clinical effectiveness of the intervention	Relapse free score	The regular lymphoma protocol demonstrated a significantly better relapse-free score than patients receiving 2 weeks of infusion protocols. There was, however, no difference seen in weekly vs. 1000 mg *2 rituximab (high dose RA protocol) in terms of rate of patients reaching complete response. Patients receiving the low-dose RA protocol demonstrated a significantly worse relapse-free score. The low-dose RA protocol additionally demonstrated a decreased frequency of patients achieving complete remission 57% vs. 85% in the standard RA protocol (P = 0.03). There was no difference seen in the rate of patients reaching complete response in patients treated with the standard lymphoma protocol vs. the standard rheumatoid arthritis protocol (1000 mg * 2). The use of adjuvant plasma exchange or immunoadsorption was associated with an increase in the time to relapse. There was no association between disease type and clinical outcomes, with 80% of both PV and PF patients achieving complete response (P = 0.95). There was likewise no association between age and clinical outcome, with the mean age for patients achieving complete response (48) and the mean age for those only achieving partial response (50) (P = 0.60). There was no association between the number of previous treatments attempted and the clinical outcome, with a mean of two previous treatments attempted in patients achieving complete remission and a mean of 1.9 treatments in those achieving incomplete response (P = 0.82).	None included	NA	Amber, K. T.; Hertl, M.. An assessment of treatment history and its association with clinical outcomes and relapse in 155 pemphigus patients with response to a single cycle of rituximab. J Eur Acad Dermatol Venereol 2015;29(4):777-782.	None included	As per primary outcome measure	Population: Age range of 4 years to 86 years. Indication is both pemphigus vulgaris and pemphigus foliaceus. Summary comments: This is systematic review with data pooled by treatment protocol: Lymphoma protocol (LP) and Rheumatoid Arthritis protocol (RA). The study had a defined objective with good patient inclusion and exclusion criteria. However, the search only included PubMed and the article doesn't mention the number of articles included or an assessment of the quality of studies. There is no information on the test for heterogeneity, publication bias or appropriate statistical methods to pool the data. The authors mention that there were number of studies where rituximab doses were as per protocols and definition of relapse was not standardised. The above limitations limit the generalisability of results.

3	Systematic + Meta Analysis	Lymphoma protocol - 184, RA protocol - 209 and modified protocol - 58	Rituximab	Clinical effectiveness of the intervention	Clinical outcome - clinical remission off therapy (CRoff), clinical remission on therapy (CRon), partial remission (PR), or non responsive (NR). Post-rituximab therapy - relapses, time to relapse, mean follow-up time, serious adverse events (SAE) and death	In summary, the results show that patients with refractory pemphigus vulgaris subgroup in the rheumatoid arthritis protocol had a significantly better clinical response, with a lesser number requiring corticosteroids or immunosuppressants but had a non-significant higher rate of relapse. There was significantly higher rate of achieving clinical remission in the high dose group compared to low dose groups, however patients in high dose group had significantly higher levels of relapse. The lymphoma protocol (n=184) - CRon: 57.6%, CRoff: 27.1%, PR: 14.6% and nearly 93% received post rituximab therapy with either corticosteroids or corticosteroids + immunosuppressants . Nearly 41% had relapse and time to relapse was 16.9 months and additional rituximab infusion for relapse was required in 24.4% patients. SAE- 9 patients and 3 deaths. The rheumatoid arthritis protocol(n= 209) : CRon: 47.3%. CRoff: 39.7%, PR: 11.4%, NR:1.4%. Nearly 40% received post rituximab therapy with either corticosteroids or corticosteroids + immunosuppressants . Relapse rate was 65.0% and time to relapse was 15.7 months and 79.9% patients received additional rituximab infusion.SAE-4 patients and 2 deaths. -	Comparison of RA protocol 500 mg vs. RA protocol 100mg	1000mg rituximab (n=188) and 500 mg rituximab(n=21) . More patients in the 500mg group had mucocutaneous disease. The frequency of use of corticosteroids and immunosuppressants was more in 1000mg group (90.4% vs 85.7%) and more patients in 1000mg group received concomitant as well post-rituximab off-label treatment compared to 500mg group. Clinical remission was similar in both groups. However, more patients in the 1000mg group were on systemic therapy in clinical remission. Partial remissions were much higher in the group of patients that got 500 mg. In the 1000mg group, 2.1% had SAE and 1% of the patients died. No SAE or deaths were reported in the 500 mg group.	Ahmed, A. Razzaque; Shetty, Shawn. A comprehensive analysis of treatment outcomes in patients with pemphigus vulgaris treated with rituximab. Autoimmun Rev 2015;14(4):323-331.	As per primary outcome measure	As per primary outcome measure	Population: Age information not given. Indication is refractory pemphigus vulgaris. Summary comments: This is a systematic review of rituximab in patients who were unresponsive to or had severe reactions from conventional treatment. All patients were treated with concomitant corticosteroids and immunosuppressant drugs of varying combination and dose so the effects of these drugs on the outcome can not be ruled out. The review included 14 retrospective case series and 27 case reports on Lymphoma protocol studies, 10 case series on the Rheumatoid Arthritis (RA) protocol and 5 case series and 6 case reports on modified protocols. The search methodology is not well described other than it was restricted to PubMed (no information on time period of the search, selection criteria , age groups and statistical methods to pool the data etc.). The conclusions drawn from the comparison between the 1000mg and 500 mg Rituximab group are not valid given the disproportionate number of patients in the two sub-groups as well as the lack of information on patient selection. The higher dose group is likely to more severely ill which could explain poorer outcomes.
3	Case series	24	Intravenous rituximab 375 mg/m2 body surface once weekly for 4 consecutive weeks	Clinical effectiveness of the intervention	Baseline and post rituximab, Pemphigus disease activity index (PDAI) score, anti-Dsg1 and anti-Dsg3 antibody titres, and CD20 positive cells fraction	The PDAI showed a significant decrease over the rituximab treatment and follow-up course ($p<0.001$). This was accompanied by decreases in anti-desmoglein 1 and anti-desmoglein 3 antibody titres over the follow-up course. The B-cell population decreased at the first follow-up, but returned to its baseline levels at the second follow-up.	None	NA	Noormohammadpour, Pedram; Ehsani, Amirhooshang; Mortazavi, Hossein; Daneshpazhooh, Maryam; Balighi, Kamran; Mofidi, Mohammad; Gholamali, Fatemeh; Sadeghinia, Ali. Rituximab therapy improves recalcitrant Pemphigus vulgaris. EXCLI J 2015;14(0):109-116.	Not included in the study	As per primary outcome	Population: Age information not given. Indication is pemphigus vulgaris. Summary comments: This is prospective case series of 24 patients with recalcitrant pemphigus vulgaris (PV) treated with rituximab. The outcome measured using PDAI, anti-DSG1 and anti-DSG3 antibody titres and CD20 positive cell fraction showed significant decreases except CD20 count which returned to baseline level at second follow-up. The study is limited by small size, patient selection and lack of patient related outcome measures.
3	Case series	10	Rituximab	Clinical effectiveness of the intervention	Partial remission, complete remission and relapse/flare.	At 16 months median period (range 8 - 36 months) follow-up, complete remission without concomitant therapy was achieved in 7 patients by a mean of 21 weeks. One patient each achieved complete remission (on immunosuppressant therapy), control of disease activity, and partial remission (on immunosuppressant therapy) by 15, 8, and 14 weeks respectively. Relapse/flare occurred in 6 patients by a mean period of 13 months. Two patients received a second cycle of rituximab infusions with good clinical response.	None included	NA	Vinay, Keshavamurthy; Kanwar, Amrinder J.; Sawatkar, Gitesh U.; Dogra, Sunil; Ishii, Norito; Hashimoto, Takashi. Successful use of rituximab in the treatment of childhood and juvenile pemphigus. J. Am. Acad. Dermatol. 2014;71(4):669-675.	Authors report infusion reactions as the most common adverse event. And there were no long-term complications.	As per primary outcome measure	Population: Age range of 9-17 years. Indication is juvenile pemphigus. Summary comments: This is a small case series of 10 children with pemphigus. The main limitations of study are its small size and lack of long-term data. However, as the disease is uncommon in children this provides useful information but generalisation is limited because of above study limitations.

3	Case series	24 patients - pemphigus vulgaris (PV) (n = 23) and pemphigus foliaceus (PF) (n = 1)	Rituximab administered using a modification of the Lymphoma regimen consisting of infusions of one injection per week for three consecutive weeks of 375 mg/m 2 and another such infusion given 3 months after the third infusion.	Clinical effectiveness of the intervention	Complete remission defined as all cutaneous and mucosal lesions completely healed (i.e. extent of disease score, 0 in pemphigus activity score (PAS)) irrespective of treatment given 6 months after the third dose of rituximab. Patients failing to show complete remission but who were responding to therapy were considered to be in partial remission. Response measured pemphigus activity score (PAS), published by the Herbst and Bystryn.	Overall, 19 (79%) patients achieved complete remission of disease, 9 out of these 19 patients were off all systemic therapy after a mean duration of 9 months (6 - 15 months). The other 10 patients had complete remission but were on no or minimal steroids and tapering doses of immunosuppressants. Out of these 10 patients, one relapsed after 6 months. Five (21%) patients had partial remission and were on low dose steroids (up to 20 mg prednisolone/day) and immunosuppressants. Of these, three patients eventually responded to treatment and showed delayed complete remission after a mean duration of 15 months (10 - 21 months). One of five patients showing partial remission relapsed in the follow-up period after 15 months.	None included	NA	Londhe, Pradnya J.; Kalyanpad, Yogesh; Khopkar, Uday S.. Intermediate doses of rituximab used as adjuvant therapy in refractory pemphigus. Indian J Dermatol Venereol Leprol 2014;80(4):300-305.	Fever with chills (n=6), hypotension(n=2), hypertension (n=1), Herpes zoster (n=2) and pulmonary embolism (n=1)	As per primary outcome measure	Population: Mean age 43.5 years. Indication is pemphigus. Summary comments: The study is limited in case selection, small sample size and long-term outcomes for those who had complete remission. As we know from other studies there is a significant number that relapse in the long-term.

Appendix Two

Literature search terms

Assumptions / limits applied to search:	
Original search terms:	-
Updated search terms - Population	Immunobullous pemphigus pemphigoid linear IgA dermatosis LAD epidermolysis bullosa acquisita EBA
Updated search terms - Intervention	Rituximab CD20 antibody, rituximab GP2013 IDEC-C2B8 IDEC-C2B8 antibody Mabthera Rituxan
Updated search terms - Comparator	Intravenous immunoglobulin IVIG Alphaglobin Endobulin Flebogamma DIF Gamimmune Gamimmune N Gamimune Gamimune N Gammagard Gammonativ Gamunex Globulin-N Immune Globulin Intravenous Intravenous immunoglobulins Intraglobin Intraglobin F Intravenous Antibodies IV Immunoglobulins Iveegam Privigen Sandoglobulin

Updated search terms - Comparator (continuation)	Venimmune Venoglobulin Venoglobulin-I Octagam Vigam mycophenolate mofetil Cellcept Mycophenolate Sodium mycophenolic acid Myfortic Sodium Mycophenolate azathioprine Azothioprine Immuran Imuran Imurel cyclophosphamide Cyclophosphane Cytophosphan Cytophosphane Cytoxan Endoxan Neosar NSC-26271 Procytox Sendoxan prednisone prednisolone dexamethasone immunoabsorption
Updated search terms - Outcome	-

Inclusion criteria	**General inclusion criteria**
	In order of decreasing priority, articles will be selected based on the following criteria. 1.All relevant systematic reviews and meta-analysis in the last 5 years and those in 5-10 years period which are still relevant (e.g. no further updated systematic review available) 2.All relevant RCTs and those in the 5-10 years period which are still relevant (e.g. not superseded by a next phase of the trial/ the RCT is one of the few or only high quality clinical trials available) >>>> If studies included reaches 30, inclusion stops here 3.All relevant case control and cohort studies, that qualify after exclusion criteria >>>> If studies included reaches 30, inclusion stops here 4.All relevant non analytical studies (case series/ reports etc.) that qualify after exclusion criteria >>>> If studies included reaches 30, inclusion stops here
	Specific inclusion criteria
	-
Exclusion criteria	**General exclusion criteria**
	Studies with the following characteristics will be excluded: 1. Does not answer a PICO research question 2. Comparator differs from the PICO 3. < 50 subjects (where studies with >50 subjects exist) 4. No relevant outcomes 5. Incorrect study type 6. Inclusion of outcomes for only one surgeon/doctor or only one clinical site (where studies with > one surgeon/doctor or one clinical site exist) 7. Narrative / non-systematic reviews (relevant referenced studies to be included)
	Specific exclusion criteria
	-