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Evidence Snapshot

The safety and clinical effectiveness of Rituximab in non-PBS indications

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Question

What is the safety and clinical effectiveness of Rituximab in non-PBS indications?
Indications include:

1. Antibody mediated rejection
2. Autoimmune haemolytic anaemia
3. IgG4 related disease (including hypophysitis, interstitial nephritis or periaortitis)
4. Immune thrombocytopenic purpura (ITP)
5. Minimal change disease
6. Nephrotic syndrome
7. Neuromyelitis optica (NMO)
8. Systemic Lupus Erythematosus (SLE)
9. Thrombotic thrombocytopenic purpura (TTP)?

Search methods

Population/Setting	Patients with the following non-PBS indications: 1. Antibody mediated rejection (AMR) 2. Autoimmune haemolytic anaemia 3. IgG4 related disease (including hypophysitis, interstitial nephritis or periaortitis) 4. Immune thrombocytopenic purpura (ITP) 5. Minimal change disease (MCD) 6. Nephrotic syndrome 7. Neuromyelitis optica (NMO) 8. Systemic Lupus Erythematosus (SLE) 9. Thrombotic thrombocytopenic purpura (TTP)
Intervention	Rituximab (RTX)
Outcomes	Safety and clinical effectiveness
Publication details	Inclusion: Synthesised data from systematic reviews (SR), meta-analysis (MA), and evidence-based guidelines. Where this was not available, evidence from randomised controlled trials was also presented. Exclusion: Retrospective case studies and case reports, commentaries, editorials
Date limitation	No limits; the most recent and updated evidence will be presented
Databases	NICE guidelines, BMJ Best practice, TRIP database, Cochrane database of systematic reviews. Where synthesised information from the above databases was unavailable, data from Pubmed clinical queries was included.
Search terms	“Rituximab” AND “indication listed as above” Search results are included in the Appendix.

Summary of findings

In this section, synthesised data on the safety and clinical effectiveness of Rituximab (RTX) is presented according to the non-PBS indications as listed above. Data from individual studies is only included for indications where no synthesised data was identified through the database search, or when more recent high quality studies (RCT) became available.

1. Antibody mediated rejection (AMR)

The evidence presented in the table below includes two high quality systematic reviews [1, 2] of which evidence was graded for its quality, and one moderate quality meta-analysis [3]. Due to limited high quality studies available at the time of publication, the systematic reviews and meta-analysis included data from abstracts and/or small trials with low methodological quality (i.e. retrospective cohort studies). The authors commented on the "poor methodological quality of its studies included". Hence the results from three recently published RCTs [4-6] are also included in the table below.

Table 1. The use of Rituximab in the treatment of antibody mediated rejection

Evidence of safety and clinical effectiveness	Source
• *Aim of systematic review* The systematic review aims to evaluate the existing evidence for the use of RTX as part of desensitisation protocols in ABO-incompatible and highly sensitised recipients. • *Results from systematic review* Two randomised controlled trials (RCTs) were identified; the remaining 19 studies were retrospective cohort studies. Twelve were reported as full papers, and nine were reported in abstract form only. • *Clinical effectiveness* Not all studies reported the effect of RTX on the incidence of AMR. Only evidence that reported incidence of AMR was presented in this report. One retrospective study compared 46 patients receiving RTX to 24 undergoing splenectomy. Five-year patient and graft survival and incidence of acute antibody-mediated rejection (AAMR) and acute T-cell mediated rejection were comparable between groups. Another three retrospective cohort study showed significant improvement effects in AMR (decreased incidence of AMR) among RTX patients as compared to other combinations of desensitisation protocols without RTX. However protocols that RTX also included plasmapheresis and intravenous immunoglobulin, making it difficult to discern how much of the benefit resulted from the addition of RTX to the protocol.	A Systematic review of the use of Rituximab for desensitisation in renal transplantation **Macklin (2014) SR [1]**
• *Aim of systematic review* The systematic review aims to determine the efficacy of treatments for acute AMR in renal allografts. Five randomised controlled trials (RCTs) and seven other controlled studies in patients with acute AMR or vascular rejection were identified. • *Efficacy* Four controlled but nonrandomised studies supported the effect of RTX. The review quoted results from another systematic review presented in abstract form that suggested that RTX was potentially effective in the treatment of refractory AMR. Given the likelihood that these studies were small and of low methodologic quality, the significance of the odds ratio is unclear; similarly, the authors concluded that an RCT was required to confirm this observation.	The treatment of acute antibody-mediated rejection in kidney transplant recipients: A systematic review. **Roberts (2012) SR [2]**

• *Aim of meta-analysis* To evaluate the effects of pre-transplantation RTX in patients. The major outcomes included antibody-mediated rejections (AMR) after kidney transplantation and one-year graft survival rate. • *Results from meta-analysis* Seven studies (n=589) were included in the meta-analysis. Four were retrospective studies, one was reported as long-term outcome and two did not state study design. • *Clinical effectiveness* Antibody-mediated rejections were reported in five studies. For the induction before renal transplantation, the AMR ranged from 0 to 30% in patients treated with RTX versus 7.4–50% in patients without RTX induction. More specifically, AMR were experienced by 17 of 182 subjects in the RTX group and 37 of 212 in the control groups. In the meta-analysis, patients treated with RTX had significantly fewer AMR (i.e., acute rejection) after kidney transplantation indicating that RTX is effective against acute rejection in kidney transplantation.	Clinical efficacy of Rituximab for acute rejection in kidney transplantation: a meta-analysis **Zhao (2014) MA [3]**
• *Aim of RCT* One-year results were reported from a phase III, multicentre, randomised, placebo-controlled trial (RITUX ERAH) that examined the effect of RTX (combined with plasmapheresis, intravenous immunoglobulin (IVIG), corticosteroids, tacrolimus and mycophenolate mofetil) on a composite measure of graft loss or absence of improvement of renal function at day 12, in patients (n=40) with biopsy-proven acute AMR. • *Efficacy* AMR occurred after a median of 35.5 days, with no advantage of RTX over control for the graft loss or renal function outcome. Both groups showed improved histological features of AMR and Banff scores at 1 and 6 months, with no significant difference between groups but with a trend in favour of the RTX group. • *Safety* In the per-protocol analysis, during the study, 37 serious adverse events were reported, 14 for patients receiving only placebo (corresponding to 7 patients), and 23 for patients receiving RTX (corresponding to 16 patients). Infections were the most frequent serious adverse events, with more urinary tract infections in the placebo group and more opportunistic infections (i.e. cytomegalovirus infection) in the RTX group. One suspected but unexpected serious adverse reaction, superficial spreading melanoma, was reported during the study in one patient who received RTX.	One-year results of the effects of Rituximab on acute antibody-mediated rejection in renal transplantation: RITUX ERAH, a multicenter double-blind randomised placebo-controlled trial **Sautenet (2016) RCT [4]**

• *Aim of RCT* In a double-blind, placebo-controlled study, 280 adult renal transplant patients were randomised between a single dose of RTX or placebo during transplant surgery to examine the effect of treatment on incidence of rejection. • *Efficacy* A single dose of RTX as induction therapy did not reduce the overall incidence of biopsy proven acute rejection, but might be beneficial in immunologically high-risk patients. Results showed that RTX-treated patients tended to have less antibody mediated rejections (AMR), compared to placebo-treated patients (4/138, 2.9% vs. 11/ 142, 7.7%, p=0.11 by Fisher's exact test). The incidence of biopsy proven acute rejection was comparable between RTX-treated (23/138, 16.7%) and placebo treated patients (30/142, 21.2%, p=0.25). Immunologically high-risk patients not receiving RTX had a significantly higher incidence of rejection (38.2%) compared to other treatment groups (RTX-treated immunologically high-risk patients, and RTX- or placebo-treated immunologically low-risk patients (17.9%, 16.4% and 15.7%, p=0.004). • *Safety* Neutropenia occurred more frequently in RTX treated patients (24.3% vs. 2.2%, p<0.001). After 24 months, the cumulative incidence of infections and malignancies was comparable. Thus leading authors to conclude that the treatment with RTX was safe.	Rituximab as induction therapy after renal transplantation: A randomised, double-blind, placebo-controlled study of efficacy and safety **Van den Hoogen (2015) RCT [5]**
• *Aim of RCT* A phase I and II randomised double-blinded placebo controlled trial examined the effect of two protocols (intravenous immunoglobulin (IVIG)+placebo versus IVIG+RTX) on rates of transplantation, AMR and renal function in 13 renal transplant patients. • *Efficacy* Results reported donor-specific HLA antibodies (DSA) rebound associated with severe AMR was seen in three patients in the IVIG+placebo group whereas no rebound was seen in the IVIG+RTX group. Renal function at 6 and 12 months showed a significant benefit for IVIG+RTX (P=0.04). The authors concluded that based on limited assessment with acknowledged limitations, both protocols appear effective in achieving levels of DSA allowable for transplantation. However, IVIG+RTX appeared more effective in preventing DSA rebound and preventing AMR and development of transplant glomerulopathy.	Benefits of Rituximab combined With intravenous immunoglobulin for desensitisation in kidney transplant recipients **Vo (2014) RCT [6]**

2. Autoimmune haemolytic anaemia

The evidence shown in the table 2 below includes a high quality evidence summary published by the National Institute for Health and Care Excellence (NICE) [7], and BMJ Best Practice Treatment Option [8].

'Evidence summaries' summarise the published evidence for selected unlicensed or off-label medicines where there are no clinically appropriate licensed alternatives. These summaries provide information for clinicians and patients to inform their decision-making and support the construction and updating of local formularies. The strengths and weaknesses of the relevant evidence are critically reviewed within the summary, but the summary is *not* NICE guidance for practice.

Table 2. The use of Rituximab in the treatment of autoimmune haemolytic anaemia

Evidence of safety and clinical effectiveness	Source
RTX and autoimmune haemolytic anaemia (Feb 2015) Limited high-quality evidence was identified that investigated how well RTX works for treating autoimmune haemolytic anaemia. One randomised controlled trial suggested that after 12 months, prednisolone plus RTX was more effective than prednisolone monotherapy for inducing a complete response to treatment in adults with newly diagnosed and previously untreated warm autoimmune haemolytic anaemia. Other uncontrolled studies suggested some effectiveness of RTX in warm and cold autoimmune haemolytic anaemia, but limitations of these studies make it difficult to draw any firm conclusions. Key points from the evidence: • *Effectiveness* ➢ An RCT in 64 adults with newly diagnosed and previously untreated warm autoimmune haemolytic anaemia suggested that after 12 months, prednisolone plus RTX was statistically significantly more effective than prednisolone monotherapy for inducing a complete response to treatment (complete response rate 75% compared with 36% respectively; p=0.003). ➢ Uncontrolled studies in people with warm autoimmune haemolytic anaemia (4 studies; n=101 in total) reported complete response rates ranging from 27% to 67%. ➢ Uncontrolled studies in people with cold haemagglutinin disease (5 studies; n=142 in total) reported complete response rates ranging from 4% to 54%. ➢ The non-randomised nature of the uncontrolled studies, differing populations, and lack of standard definitions for response to treatment make it difficult to draw any firm conclusions from this evidence. • *Safety* ➢ The summary of product characteristics (SPC) for RTX describes that infusion related reactions are very common (more than 1 in 10) in people treated with intravenous RTX. Severe infusion related reactions with a fatal outcome have been reported in post marketing use. ➢ Serious infections, including fatalities, can occur during RTX therapy, and RTX is contraindicated in people with an active, severe infection, and in people who are severely immunocompromised. ➢ Very rare cases of fatal progressive multifocal leukoencephalopathy have been reported after using RTX and people should be monitored at regular intervals for any new or worsening neurological symptoms or signs suggestive of this condition. ➢ In the RCT, the most commonly reported adverse events in people in the prednisolone monotherapy and prednisolone plus RTX groups were dyspnoea (16.7% compared with 13.3% respectively), fatigue (13.3% in both groups), headache (13.3% compared with 6.7% respectively), dyspepsia (13.3% compared with 3.3% respectively) and insomnia (10% in both groups).	**NICE Evidence Summary [ESUOM39] [7]**

RTX before splenectomy (April 2016) RTX is not approved for any subtype of haemolytic anaemia but has demonstrated significant activity in patients' refractory to other therapies. (Evidence C) It is a reasonable option prior to splenectomy. It may be used as frontline therapy when combined with corticosteroids in patients with warm antibody reactive autoimmune haemolytic anaemia. Evidence score: Poor-quality evidence, from a retrospective study of 36 patients with autoimmune haemolytic anaemia refractory to other treatments, that RTX therapy is associated with a clinical response (77% of patients). All patients achieving a complete response (61%) maintained this response for >6 months. **Evidence C – based on poor quality observation (cohort) studies or methodologically flawed randomised controlled trials (RCTs) of <200 participants*	**BMJ Best Practice Treatment Option [8]**

3. IgG4 related disease (including hypophysitis, interstitial nephritis or periaortitis)

No synthesised data from high quality studies was identified for the use of RTX in the treatment of the hypophysitis, interstitial nephritis or periaortitis. Two single case reports [9,10] were identified and excerpts from their abstracts are presented in the table below. Limited information on the safety or efficacy of RTX in hypophysitis and interstitial nephritic is detailed in the abstracts.

Table 3. The use of Rituximab in the treatment of IgG4 related disease

Evidence of safety and clinical effectiveness	Source
Summary of abstract One case report on a female treated with RTX for lymphocytic hypophysitis showed improvement in vision within a few weeks. There was no clinical or radiographic exacerbation two years after starting immunotherapy. RTX, an anti-CD20 antibody that specifically depletes B lymphocytes, can be an effective treatment strategy for patients with steroid-refractory, B cell-predominant lymphocytic hypophysitis.	Novel strategy to treat a case of recurrent lymphocytic hypophysitis using Rituximab **Schreckinger (2012) Case report [9]**
Summary of abstract One case report on a patient who received RTX for treatment of IgG4-Related Tubulointerstitial Nephritis. He was refractory to treatment with prednisone. The patient received Rituximab and had prompt sustained improvement in renal function. At one year post RTX treatment, his serum creatinine remains at baseline and imaging study revealed reduction in his kidney size. This is the first case report using RTX as a steroid sparing option for refractory IgG4-tubulointerstitial nephritis. More information is needed on the long-term effects of using of B-cell depleting agents for glucocorticoid resistant IgG4-tubulointerstitial nephritis.	Rituximab for the Treatment of IgG4-related tubulointerstitial nephritis: case report and review of the literature. **McMahon (2015) Case report [10]**

4. Immune thrombocytopenic purpura

The evidence shown in the table below includes a high quality *evidence summary published by the National Institute for Health and Care Excellence (NICE) [11] and BMJ Best Practice Ongoing Treatment Option [8].

'Evidence summaries' report published evidence for selected unlicensed or off‐label medicines where there are no clinically appropriate licensed alternatives. These summaries provide information for clinicians and patients to inform their decision‐making and support the construction and updating of local formularies. The strengths and weaknesses of the relevant evidence are critically reviewed within the summary, but the summary is not NICE guidance.

Table 4. The use of Rituximab in the treatment of immune thrombocytopenic purpura

Evidence of safety and clinical effectiveness	Source
RTX and idiopathic thrombocytopenia purpura (October 2014) Most of the evidence for using RTX in adults with immune thrombocytopenic purpura comes from observational studies, with no comparator arm. The populations in the included studies varied, as did the platelet count considered to represent an overall response or complete response. The randomised controlled trials (RCTs) discussed in this evidence summary had a number of limitations, including small numbers of participants. All of these factors make it difficult to draw firm conclusions from the evidence. The evidence for efficacy of RTX in children and young people is weaker, drawn from case series and 1 cohort study with no comparator arm. • *Effectiveness* ➢ A systematic review of mainly observational studies (n=368) suggests that RTX can increase platelet levels in adults with immune thrombocytopenic purpura; although response rates varied significantly between individual studies. No comparisons with other treatments were made. ➢ An RCT (n=137) suggests that RTX plus dexamethasone may be better than dexamethasone alone for achieving a sustained response in terms of increased platelet levels in adults with newly diagnosed primary immune thrombocytopenic purpura. ➢ Another RCT (n=60) shows that RTX is no better than placebo for preventing treatment failure in adults with immune thrombocytopenic purpura once standard treatment was stopped. ➢ A retrospective cohort study (n=105) suggests that there is no difference between RTX and splenectomy for the composite outcome of death from, or hospitalisation for, bleeding or infection in adults with immune thrombocytopenic purpura. ➢ In children and young people with immune thrombocytopenic purpura, a systematic review (n=352) suggests that RTX can increase platelet levels. However included studies were all observational, limiting the conclusions that can be drawn. • *Safety* ➢ The summary of product characteristics (SPC) for RTX describes that infusion related reactions are very common in people treated with intravenous RTX. Severe infusion related reactions with a fatal outcome have been reported in post-marketing use. ➢ Serious infections, including fatalities, can occur during RTX therapy, and RTX is contraindicated in people with an active, severe infection, and in people who are severely immunocompromised. ➢ Very rare cases of fatal progressive multifocal leukoencephalopathy have been reported after use of RTX and people should be monitored at regular intervals for any new or worsening neurological symptoms or signs suggestive of this condition.	**NICE Evidence Summary [ESUOM35] [11]**

RTX and idiopathic thrombocytopenia purpura (June 2015) • *Effectiveness* For use in non-pregnant adults: refractory to initial medical treatment nonsurgical candidate or with failed splenectomy, for the treatment of ongoing idiopathic thrombocytopenic purpura. In a systematic review, RTX allowed response in platelet counts >50 x 10^9/L (>50 x 10^3/microlitre) in 62.5% of adult patients with ITP. A meta-analysis restricted to studies investigating the use of RTX before splenectomy failed to show an improvement in the overall and complete response rates above the figures reported in the literature for mixed series including splenectomised and non-splenectomised patients. RTX treatment remains off-label. However, long-lasting response (3 years or longer) is in the range of 15% to 20%. Moreover, one randomised trial comparing the use of adjuvant RTX in non-splenectomised patients showed no differences in outcome (platelet count increase; rate of significant bleeding; rescue treatment) versus placebo. • *Safety* Use of this agent before splenectomy is severely limited by significant toxicities, including up to 2.9% deaths and concern about an increased risk of progressive multifocal leukoencephalopathy (PML) in patients with autoimmune disorders treated with this agent. There are also some concerns about pregnancy outcomes after maternal exposure to RTX.	**BMJ Best Practice Ongoing Treatment Option [8]**

5. Minimal change disease (MCD)

Limited high quality evidence was available for the use of RTX in the treatment of MCD. The evidence included a low to moderate quality systematic review [12] which was based mainly on retrospective studies that were not appraised or graded for quality. Evidence published from the BMJ Best Practice Emerging Treatment was also limited and included case reports and small prospective studies [8].

Table 5. The use of Rituximab in the treatment of minimal change disease

Evidence of safety and clinical effectiveness	Source
RTX and minimal change disease (Jul 2015) • *Efficacy* ➢ Safety and efficacy of RTX were assessed among patients ages 6 to 22 years with severe corticosteroid-dependent nephrotic syndrome (NS) or corticosteroid-resistant but ciclosporin (cyclosporine)-sensitive idiopathic NS. ➢ Peripheral B cells were depleted in all patients. Remission was induced in three of the seven proteinuric patients. One or more immunosuppressive treatments could be withdrawn in 85%, with no relapse of proteinuria and without increasing other drugs. RTX was effective in all patients when given during a proteinuria-free period in association with other immunosuppressive agents. ➢ Thirteen of 16 adult patients (19-73 years) with multi-relapsing, corticosteroid-dependent, or corticosteroid-resistant MCD experienced complete remission following RTX therapy. Two patients reached partial remission and 1 had no response to therapy. Eight patients remained in remission during 12 to 70 months of follow-up (median 44 months). Seven relapsed after 9 to 28 months, with repeated RTX treatment in 4 of these. ➢ RTX therapy was associated with maintenance of complete remission, including 10 of the 11 patients who showed B-cell repletion following discontinuation of RTX therapy. In one case report, complete disease remission with RTX in corticosteroid- and cyclophosphamide-resistant nephrotic syndrome was sustained for more than 32 months despite CD19 recovery. ➢ Controlled trials are needed to confirm these findings.	**BMJ Best Practice Emerging Treatment**

• *Aim of systematic review* The systematic review aims to summarise data from pre-existing studies reporting the outcome of RTX treatment in patients with MCD and focal segmental glomerulosclerosis (FSGS). • *Results of systematic review* The evidence included two prospective and twelve retrospective studies (n=86 patients, n=77 diagnosed with MCD) of which studies were not appraised for its quality. • *Effectiveness* Response to treatment defined as complete or partial remission was evaluated in 80 patients, since we were not able to obtain information on the response rate of 6 patients. Out of those 80 patients, 78 achieved at least partial remission, while two patients were non-responsive to RTX treatment. Of the patients with detailed reports on response rates, all but 1 patient with MCD (72 out of 73) was responsive to RTX therapy. • *Adverse events* No severe adverse events have been reported in the analysed patients receiving RTX due to frequently relapsing or steroid-dependent MCD or FSGS. Infusion-related reactions were frequently reported and consisted of transient hypotension, itchy red eyes, cough, hiccough, and exanthema. Long-term complications have been observed less commonly and consisted of mild leukopenia in 1 case. In the report treating several glomerulonephritis patients with RTX, about half of the patients experienced infusion reactions (hypotension, bradycardia, chest tightness, body ache) and 1 patient suffered from bronchopneumonia two months after RTX.	Rituximab treatment for relapsing minimal change disease and focal segmental glomerulosclerosis : a systematic review **Kronbichler 2014 SR [12]**

6. Nephrotic syndrome (NS)

Limited evidence from a Cochrane review [13] and BMJ Best Practice [8] was available on the use of RTX in the treatment of nephrotic syndrome. Data published in the BMJ Best Practice Emerging Treatments was limited to three studies, two of which were RCTs. As the information presented in BMJ Best Practice did not mention the results of the RCT, hence the abstracts of the two referenced RCTs were obtained and their conclusions summarised for the purpose of this report. The most updated evidence from the Cochrane review [13] was based on findings from a small single-centre RCT.

Table 6. The use of Rituximab in the treatment of nephrotic syndrome

Evidence of safety and clinical effectiveness	Source
RTX and Nephrotic syndrome (Feb 2016) Treatment with RTX has been suggested for lupus nephritis resistant to conventional therapies. There is increasing evidence for its potential use in frequent relapsing and corticosteroid-dependent NS. More studies need to be conducted to prove efficacy. • *Results from abstracts of the two RCTs* One RCT (n=30) showed that RTX treatment was non-inferior to steroid in the treatment of juvenile steroid-dependent NS, while the other RCT (n=52) reported that the median relapse-free period was significantly longer in the RTX group (267 days, 95% CI 223-374) than in the placebo group (101 days, 70-155; hazard ratio: 0·27, 0·14-0·53; p<0·0001). Ten patients (42%) in the RTX group and six (25%) in the placebo group had at least one serious adverse event (p=0·36).	**BMJ Best Practice Emerging Treatments [8]**
• *Aim of systematic review* To evaluate the benefits and harms of different immunosuppressive medications, other than corticosteroids, that are used in children who pursue a relapsing course of steroid-sensitive nephrotic syndrome (SSNS). • *Effectiveness* In steroid- and cyclosporine-dependent disease, RTX significantly reduced the risk of relapse at three months compared with conventional therapy. This was based on a small single-centre RCT (n=54) with very low risk of bias. The study comparing treatments with RTX plus cyclosporin and prednisolone versus cyclosporin and prednisolone suggested that RTX was a valuable addition in children with steroid and calcineurin-dependent nephrotic syndrome. The primary outcome in this study was proteinuria at three months; this was reduced by 70% in children who received RTX. • *Adverse events* The reported adverse effects of RTX were bronchospasm, hypotension, fever, skin rash and joint pain.	Non-corticosteroid immunosuppressive medications for steroid-sensitive nephrotic syndrome in children (Review) **Pravitsitthikul Systematic Review 2013 [13]**

7. Neuromyelitis optica (NMO)

Limited synthesised data was identified for the use of RTX in the treatment of neuromyelitis optica. A report published by the McGill University Health Centre [14] was based only on case reports and case series while results from an ongoing systematic review were not available at this point in time.

Table 7. The use of Rituximab in the treatment of neuromyelitis optica

Evidence of safety and clinical effectiveness	Source
Technology Assessment Unit of McGill University Health Centre (MUHC). The effectiveness and safety of RTX (anti-CD20) in neurologic autoimmune diseases. Report:64 (August 2013) • *Aim of the report* To review the efficacy and cost impact of the use of RTX in neurologic autoimmune diseases. • *Results of the report* No systematic reviews or HTAs were identified, and the evidence presented in the report above consisted of case series, case reports, complete reports and abstracts as well. • *Efficacy* Fifteen case series (n=250), and case reports (n= 22 patients) were included. The majority of patients with NMO had clinical improvement following treatment with RTX, as measured by frequency of relapse and disability. A summary of individual patient data from case series that 104/114 (91%) patients had less frequent relapses and that RTX reduced the annualised relapse rate from a median 1.8 per year (range 0.13 to 12) before treatment to a median of 0 (range 0 to 15.6) post-treatment. In the case reports, 8/20 patients were reported as having improved with RTX. • *Adverse events* Five of 162 patients died, two of severe NMO relapse and three of infection, and three patients were hospitalised due to possibly related adverse events (two infections). There were no adverse events of an unexpected type. Given the small number of patients, and the morbidity and mortality of the disease itself, it is difficult to assess whether RTX increased the risk of death or hospitalisation.	The effectiveness and safety of Rituximab (anti-CD20) in neurologic autoimmune diseases **MUHC 2013 [14]**
One systematic review was identified (PROSPERO); the author confirmed that the review was not available at this point in time.	The effectiveness of Rituximab for the treatment of neuromyelitis optica: a systematic review **Bourke (ongoing)**

8. Systemic Lupus Erythematosus (SLE)

Synthesised evidence was identified from the BMJ Best Practice emerging treatment [8], two systematic reviews and one meta-analysis. The most updated systematic review was of high quality and included synthesised data from earlier reviews. Hence only data from the most recent systematic review [15], that was appraised and graded by the authors, is presented in the table below.

Table 8. The use of Rituximab in the treatment of systemic lupus erythematosus

Evidence of safety and clinical effectiveness	Source
RTX and SLE A chimeric human-murine monoclonal antibody directed against CD20 on B cells and their precursors; not directed against plasma cells. Mechanisms other than B-cell depletion are thought be equally important in its action in SLE. Can be useful in cases resistant to initial therapy with conventional regimens and has the potential to produce long remissions in SLE after two to four infusions. A number of described regimens include giving RTX with intravenous cyclophosphamide (omitting this if previous toxicity, leukopenia, or infection), mesna (uro-protective agent), and fluids. This should be repeated two weeks later. Sustained beneficial effects in open studies have reported benefit in musculoskeletal, mucocutaneous, renal, and haematological manifestations of SLE, but these benefits have not been confirmed in double-blind randomised phase II/III trials. More favourable results were observed in African-American and Hispanic people. Despite the lack of favourable results from RCTs, a systematic review suggests that RTX may be of benefit in lupus nephritis refractory to standard therapies.	**BMJ Best Practice Emerging treatment [8]**
• *Aim of systematic review* To analyse the efficacy and safety of RTX in the treatment of non-renal systemic lupus erythematosus (SLE) in non-paediatric populations. • *Results of systematic review* The systematic review included one RCT and its explanatory analysis, two open label studies and 22 cohort studies (15 prospective). Of the 1231 patients included, most of them were women aged 15 to 84 years with active disease refractory to glucocorticoids and/or immunosuppressant (ISS) drugs. Dosing and infusion regimens were variable and in most studies, glucocorticoids and non-biologic ISS drugs were concomitant treatments. • *Efficacy* There is acceptable evidence to support the use of RTX for clinical improvements and response to disease activity in patients with non-renal SLE (Grade B), and regarding the efficacy in B cell depletion (Grade B) and in positive anti-donor specific DNA patients (Grade B) to reduce steroid doses (Grade B). RTX has been shown to be safe and effective in the treatment of non-renal SLE especially in terms of disease activity, immunologic parameters and steroid-sparing effect. However, it can only be recommended for organ-specific manifestations such as arthritis and thrombocytopaenia. High-quality studies are needed in order to consider the long-term effects of re-treatment on different organ-specific manifestations. • *Safety* Adverse events were reported in one RCT, two open studies and 20 cohort studies. The most frequent adverse events were infusion reactions and infections. One RCT reported no differences compared with placebo in overall adverse events, infections or serious infections. But there were differences regarding infusion reactions, neutropenia and herpes virus infections. The incidence of serious infections was estimated at 6.6/100–12.6/100 patient-years. The authors concluded that there was enough evidence on the short-medium term safety of RTX based on good quality studies. **Grade B: consistent evidence based on Level 2 (i.e. SR on cohort studies, individual cohort study, low quality RCTs or "outcomes" research) and Level 3 (i.e. SR of case-control studies, individual case control studies) or from extrapolations from Level 1 (i.e. SR of RCT or individual RCT) studies.*	Efficacy and safety of Rituximab in the treatment of non-renal systemic lupus erythematosus: A systematic review **Cobo-Ibanez (2014) SR [15]**

9. Thrombotic thrombocytopenic purpura (TTP)

High quality evidence for the use of RTX in the treatment of thrombotic thrombocytopenic purpura was scarce. The BMJ Best Practice treatment option does not provide details of the safety or efficacy of RTX and evidence was limited to mainly case reports and case series as no RCTs were identified. Findings from only the most recent review [16] were presented. The review was of high quality and its evidence was graded based on study design of included studies. The reviewers ranked the overall quality of evidence available as being low.

Table 8. The use of Rituximab in the treatment of thrombotic thrombocytopenic purpura

Evidence of safety and clinical effectiveness	Source
RTX and TTP Acute episode of TTP RTX is a monoclonal anti-CD20 antibody that targets B-cell populations. It is used frequently for the treatment of B-cell non-Hodgkin's lymphoma. Studies have been evaluating it in autoimmune processes including TTP because it is a relatively safe and easy method for targeting antibody production. RTX is becoming more commonly used than the other immunosuppressive agents in the US.	**BMJ Best Practice Treatment Option**
Aim of review The review aims to investigate the appropriate role of rituximab in the management of patients with TTP during the three periods: (1) for initial treatment of an acute episode, together with plasma exchange (PEX) and corticosteroids; (2) for treatment of a refractory episode (unsatisfactory response to initial treatment with PEX and corticosteroids), and (3) for prophylaxis in asymptomatic patients with severe ADAMTS13 deficiency following recovery but no clinical evidence of TTP to prevent relapse. *Results* Seventeen publications were included in the review of which three were cohort studies, and 15 cases series/reports. This included data from more than 270 patients. *Efficacy* We suggest rituximab be considered for initial treatment with PEX and corticosteroids in patients who present with an acute episode of TTP (Grade 2C): In patients with an acute episode of TTP, initial treatment with rituximab, PEX, and corticosteroids appeared to result in a remission in >90% of patients within 14 to 21 days. Rituximab may decrease the frequency of subsequent relapses. We recommend rituximab for patients who have a refractory episode of TTP despite PEX and corticosteroids (Grade 1C): In patients with an episode of refractory TTP, addition of rituximab to PEX and corticosteroids increases platelet counts in >80% of patients and may decrease the time required to achieve a platelet count response. The frequency of relapse in rituximab-treated patients may be decreased compared with control patients in the short term, but may also represent a delay in relapse and not differ from control patients in long-term follow-up. We recommend against the use of rituximab in asymptomatic patients who have a severe deficiency of ADAMTS13 activity but no clinical evidence of TTP (grade 1C): Prophylactic treatment with rituximab may result in fewer TTP relapses, although follow-up was longer in control patients, favouring detection of relapse.25 In the largest study, 30% of patients had asymptomatic decreased ADAMTS13 activity during follow-up after initial prophylactic rituximab and received additional rituximab or other treatments, some of which have greater risks than rituximab.25 In some asymptomatic patients, sustained ADAMTS13 activity recovery does not occur even with multiple rituximab treatments. The effect of a single course of rituximab cannot be assessed. **The GRADE (Grading of Recommendations Assessment, Development, and Evaluation) system was used to classify recommendations as strong (grade 1) or weak (grade 2) based on the balance of benefits and risks and the confidence in these estimates. Patient values and preferences may influence the interpretation of management recommendations. The quality of evidence was classified as high (grade A), moderate (grade B), or low (grade C) based on the study design, consistency of results, and directness of the evidence.*	The role of rituximab in the management of patients with acquired thrombotic thrombocytopenic purpura **Lim 2015 Review [16]**

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Appendix – Search Results

Table A-1. Antibody mediated rejection

Database	Results
NICE	"RTX" AND "antibody mediated rejection" = nil "RTX" AND "antibody mediated rejection" = nil
BMJ	"RTX" AND "antibody mediated rejection"; screened results 68 = nil
TRIP	(title:antibody mediated rejection)(title:RTX) Excluded: 2 SR and 1 retrospective study Included: Sautenet (2016) RCT
Cochrane	"antibody mediated rejection" Include: Macklin 2014 SR
Pubmed Clinical Queries	"antibody mediated rejection RTX" = 8 reviews, 9 clinical studies Included: Roberts (2012) SR & Zhao (2014) MA, van den Hoogen (2015) RCT, Vo (2014) RCT

Table A-2. Autoimmune haemolytic anaemia

Database	Results
NICE	"Autoimmune haemolytic anaemia" Included: Evidence summary [ESUOM39]
BMJ	"Autoimmune haemolytic anaemia" Included: Treatment option
TRIP	"Autoimmune haemolytic anaemia" Information already included in the above summaries

Table A-3. IgG4 related disease (including hypophysitis, interstitial nephritis or periaortitis)

Database	Results
NICE	"hypophysitis", "interstitial nephritis", "periaortitis" = nil
BMJ	"hypophysitis", "interstitial nephritis", "periaortitis" = nil
TRIP	(hypophysitis)(RTX) = 1 case report (interstitial nephritis)(RTX) screened 53 = 1 case report "periaortitis Exclude: Zaidan (2011)
Pubmed Clinical Queries	"hypophysitis RTX" = nil "interstitial nephritis RTX" = 2 clinical studies "periaortitis RTX" = nil Included: Schreckinger 2014, McMahon 2012

Table A-4. Immune thrombocytopenic purpura (ITP)

Database	Results
NICE	"Immune thrombocytopenic purpura" Included: Evidence Summary [ESUOM35]
BMJ	"Immune thrombocytopenic purpura" Included: Ongoing treatment option
TRIP	"Immune thrombocytopenic purpura" Information already included in the above

Table A-5. Minimal change disease

Database	Results
NICE	RTX AND "minimal change disease" = nil "minimal change disease" = nil
BMJ	"Minimal change disease" Included: Emerging treatment, prognosis
TRIP	"Minimal change disease" Included: Kronbichler 2014 SR

Table A-6. Nephrotic syndrome

Database	Results
NICE	“nephrotic syndrome”; screened results 19 = nil
BMJ	“nephrotic syndrome” Emerging treatment for Glomerulonephritis
TRIP	“nephrotic syndrome” Results: 1 SR 2013 and 1 2007 HTA Included: Pravitsitthikul 2013 SR

Table A-7. Neuromyelitis optica

Database	Results
NICE	“Neuromyelitis optica” = nil
BMJ	“Neuromyelitis optica” = nil
TRIP	(title:Neuromyelitis optica)(title:RTX) Not available: 1 ongoing SR; results not available at time of this review Included: MUHC 2013
Cochrane	“rituximab” AND “neuromyelitis optica”; screened results 5 = nil

Table A-8. Systemic Lupus Erythematosus (SLE)

Database	Results
NICE	“RTX” AND “Systemic Lupus Erythematosus” = nil
BMJ	“RTX” AND “Systemic Lupus Erythematosus” Included: Emerging treatment
TRIP	(title:SLE or systemic lupus)(title:RTX); screened results 35 = 1 Not available: Hayes Inc HTA
Cochrane	“RTX AND “SLE or systematic lupus” Included: Cobo-Ibanez 2014 SR Excluded: Lan 2012 SR & Duxbury 2013 SR

Table A-9. Thrombotic thrombocytopenic purpura (TTP)

Database	Results
NICE	“Thrombotic thrombocytopenic purpura” = nil
BMJ	“Thrombotic thrombocytopenic purpura” Included: Treatment Option
TRIP	(title:Thrombotic thrombocytopenic purpura)(title:RTX) screened results 23 = nil
Cochrane	“Thrombotic thrombocytopenic purpura” AND “RTX” screened results 10 = 3 Excluded: Michael 2009 SR
Pubmed Clinical Queries	“Thrombotic thrombocytopenic purpura rituximab” Included: Lim 2015 Review Excluded: Tun 2012 SR