New Medicine Recommendation

Rituximab Intravenous Infusion for the Treatment of Autoimmune Haemolytic Anaemia (AIHA) in Adults

Recommendation: Red

Rituximab is recommended as an alternative treatment for adults with AIHA where patients are contraindicated to or fail to respond to standard active treatments (e.g. corticosteroids).

Treatment requires initiation and continuation by specialist haematology services.

Summary of supporting evidence:

- Available RCT evidence demonstrated improved response rates with rituximab in patients with AIHA.
- The place in therapy of rituximab in AIHA has been defined by recent British Society of Haematology guidelines.
- Rituximab is usually given as a single course of treatment and is intended to induce long term remission of AIHA.
- Rituximab has been available as a licensed medicine in the UK since 1998 and has an extensive pool of safety data.
- Rituximab may be preferred to alternative treatment options such as invasive splenectomy or the use of cytotoxic medicines.
- The continued introduction of biosimilar preparations of rituximab may enable more cost-effective treatment regimens.
- Patients would be required to attend hospital weekly for four weeks to be administered an intravenous infusion of rituximab over several hours.

Details of Review

Name of medicine (generic & brand name)**:** Rituximab (MabThera®, Truxima® and Rixathon®) [1]

Strength(s) and form(s): 100mg and 500 mg concentration for solution for infusion (also available as 1400mg solution for subcutaneous injection which is not routinely used in AIHA) [1]

Dose and administration: Unlicensed indication: Most commonly cited dose in the studies included in this evidence review is:

375mg/m^2 body surface area weekly for four weeks.

(A minority of studies used a lower fixed dose of rituximab 100mg weekly for four weeks). [2]

BNF therapeutic class / mode of action: Antineoplastic drugs, monoclonal antibodies.

Rituximab triggers mediation of B-Cell lysis through complement / antibody dependent cytotoxicity and CD20 induced apoptosis. [1]

Licensed indication(s): Rituximab is indicated in adults for the following indications:

Non-Hodgkin's lymphoma (NHL)

The treatment of previously untreated patients with stage III-IV follicular lymphoma in combination with chemotherapy.

Maintenance therapy is indicated for the treatment of follicular lymphoma patients responding to induction therapy.

Monotherapy is indicated for treatment of patients with stage III-IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy.

The treatment of patients with CD20 positive diffuse large B cell non-Hodgkin's lymphoma in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) chemotherapy.

Chronic lymphocytic leukaemia (CLL)

In combination with chemotherapy for the treatment of patients with previously untreated and relapsed/refractory CLL.

Rheumatoid arthritis

In combination with methotrexate for the treatment of adult patients with severe active rheumatoid arthritis who have had an inadequate response or intolerance to other disease-modifying anti-rheumatic drugs (DMARD) including one or more tumour necrosis factor (TNF) inhibitor therapies.

Granulomatosis with polyangiitis and microscopic polyangiitis

In combination with glucocorticoids for the induction of remission in adult patients with severe, active granulomatosis with polyangiitis (Wegener's) (GPA) and microscopic polyangiitis (MPA).

Proposed use (if different from, or in addition to, licensed indication above): The treatment of autoimmune haemolytic anaemia in adults.

Course and cost: 375mg/m^2 body surface area weekly for four weeks.

For an adult with a body surface area of 1.86 m^2 the total 4-week dose:

= 1.86 x 375 x 4

= 2790mg

Assuming wastage this would require 700mg of rituximab weekly (1 x 500mg vial and 2 x 100mg vial) for 4 weeks.

Cost based on MIMs May 2018 prices (Contract prices may vary within hospital trusts)

MabThera® 1x500mg vial = £873.15

MabThera® 2x100mg vial = £349.25

Total cost of MabThera® = (873.15 + 349.25) x 4 weeks = £4,889.60

Truxima® / Rixathon® 1x500mg vial = £785.84

Truxima® / Rixathon® 2x100mg vial = £314.33

Total cost of Truxima® / Rixathon® = (785.84 + 314.33) x 4 weeks = £4,400.68

(Rituximab is usually given as a single course of treatment to induce long-term remission, however further treatment with rituximab may be given to patients who relapse following initial response. The cost of treatment may therefore be higher than stated). [2]

Current standard of care/comparator therapies:

- Corticosteroids (1st line treatment).
- Elective splenectomy.
- Immunosuppressive drugs azathioprine, ciclosporin, danazol, mycophenolate and vinca alkaloids. [3]

For cold haemagglutinin disease, corticosteroids, elective splenectomy and conventional immunosuppressants appear to be less effective. Based on current published data, rituximab is considered the 1st line treatment. [4]

Relevant NICE guidance:

NICE evidence summary (ESUOM39): Autoimmune haemolytic anaemia: rituximab.

Background and context

Autoimmune haemolytic anaemia (AIHA) is a decompensated acquired haemolysis caused by the host's immune system acting against its own red blood cell antigens. Patients with AIHA may present with symptoms of anaemia (weakness 88%, dizziness 50%, dyspnoea 9%), haemolysis (jaundice 21%, dark urine 3%) or symptoms of an underlying disorder. Without underlying disease, examination may be unremarkable or reveal mild pallor or splenomegaly. Less often, severe haemolysis leads to hepatosplenomegaly, haemoglobinuria and signs of heart failure. Diagnosis is usually based on the presence of blood markers indicating haemolysis, review of a blood smear with features consistent with the diagnosis and evidence of anti-erythrocyte antibodies (autoantibodies), detectable by the direct antiglobulin test. [3]

The condition is normally divided into warm and cold antibody types. Warm antibody type can be primary or secondary to other conditions such as systemic lupus erythematosus, lymphoma, chronic lymphocytic leukaemia or Evans syndrome. Cold antibody type is more often secondary to another condition, such as lymphoma. Cold antibody types include cold haemagglutinin disease and paroxysmal cold haemoglobinuria. In warm antibody type, autoantibodies react at 37ºC. In cold antibody type, autoantibodies react at lower temperatures of 20ºC or below. [2]

The incidence of AIHA is approximately 1 per 100,000 population per year. It can occur at any age but incidence rises with increasing age. [3]

The British Society for Haematology recommends rituximab as a second-line treatment for warm AIHA, mixed AIHA and paroxysmal cold haemoglobinuria following failure to respond to first-line corticosteroids. In cold haemagglutinin disease, rituximab is suggested as a first-line treatment (in combination with fludarabine if clonal disorder). [3]

For warm autoimmune haemolytic anaemia, first-line treatment is normally with corticosteroids which are effective in 70−85% of people. Splenectomy and off-label conventional immunosuppressive drugs have been traditionally used as second-line treatments, and recently rituximab has also been used as a second-line treatment option. If treatment is required in cold haemagglutinin disease, corticosteroids, splenectomy and conventional immunosuppressants are much less effective, and over the last 10−15 years, on the basis of limited published data, rituximab has become first-line treatment. [4]

The mechanism of action of rituximab in AIHA is not fully understood. Investigations indicate that rituximab's effects on T-cell regulation may play a major role in its mechanism of action for treating AIHA. [5]

Summary of evidence

Summary of efficacy data in proposed use:

There are two randomised controlled trials (RCTs); and one meta-analysis of a single RCT and 20 uncontrolled studies. Most studies used intravenous rituximab at a dosage of 375mg/m^2 body surface area weekly for four weeks. Clinical efficacy evidence related to either warm AIHA, cold AIHA or mixed types of AIHA.

Warm AIHA

Reynaud et al meta-analysis [6]

This meta-analysis evaluated the response to rituximab treatment in a total of 409 AIHA patients (with both warm and cold types of AIHA). **Reynaud et al** extracted data from the RCT conducted by **Birgens et al** (described below) and 20 uncontrolled studies with separate reported data for the warm and cold types of AIHA.

For warm AIHA, data from 11 studies (n=154) demonstrated the overall response rate to rituximab was 79% (CI95% 60; 90) and the complete response rate was 42% (CI95% 27; 58).

Birgens et al. RCT [7]

This was a multicentre, randomised, open-label phase III trial of 64 adult participants with newly diagnosed or previously untreated warm AIHA. The RCT included patients with primary AIHA and AIHA secondary to concomitant autoimmune disease or low-grade B-cell lymphoproliferative neoplasia. Patients were excluded from the trial if their AIHA was drug induced; they had previous treatment with rituximab or immunosuppressant drugs within the last three months; autoimmune disease developed within the last six months; they suffered other serious diseases (including malignancy); had hypersensitivity to the active substance; had an active infection; were pregnant or breastfeeding.

All patients received prednisolone 1.5mg/kg/day for two weeks, followed by 0.75mg/kg/day for one week then 0.5mg/kg/day for one week. Patients were gradually reduced over the next four to eight weeks to the lowest dose of prednisolone that was effective in maintaining a normal haemoglobin level. Patients were randomised 1:1 to either receive prednisolone monotherapy or prednisolone combined with rituximab.

The primary objective of the study was to measure differences at 3, 6 and 12 months in complete response (normalisation of haemoglobin concentration without ongoing immunosuppressants and biochemical signs of haemolytic activity) and partial response (as for complete response although patient requiring continued low dose prednisolone [<10mg/day] or patient achieving a stable, acceptable haemoglobin level without the need for any treatment [except for low dose prednisolone]). Secondary outcome measures included relapse-free survival.

At 3 and 6 months after treatment, there was no statistically significant difference in any response (complete or partial) between the prednisolone monotherapy and the prednisolone plus rituximab groups. After 12 months, participants reported only a complete response or persistent disease. The complete response rate was 36% (CI95% 19; 56) in the people still alive at 12 months in the prednisolone monotherapy group, compared with 75% (CI95% 55; 89) in the people still alive at 12 months in the prednisolone plus rituximab group. The difference between the groups was statistically significant (p=0.003).

The secondary outcome of relapse-free survival in people whose condition had shown any response to treatment (complete or partial) was statistically significantly lower in the prednisolone monotherapy group compared with the prednisolone plus rituximab group (hazard ratio 0.33, [CI95% 0.12; 0.88, p=0.02]).

Michel et al RCT [8]

This was a 2-year follow up, phase III prospective randomised, double-blind, placebo-controlled, multicentre trial of 39 adult patients with warm AIHA. Eligible patients were randomized in a 1:1 ratio (double-blind) to receive two infusions of rituximab or placebo at a fixed dose of 1,000 mg

2-week apart, on Days 1 and 15 after randomisation. The main exclusion criteria were (prior treatment with rituximab; warm AIHA treated for >6 weeks with corticosteroids; ongoing or recent treatment with immunosuppressants (within <2 weeks); associated non- Hodgkin lymphoma (except for stage A chronic lymphocytic leukaemia); systemic lupus erythematosus with extra-hematologic manifestations requiring treatment; any other associated cause of hereditary or acquired haemolytic anaemia; (7) negative direct antiglobulin test (DAT) result, DAT with C3d positivity alone and/or definite diagnosis of cold agglutinin disease; positive HIV and/or hepatitis B/C virus test result; neutrophil count $<1.0 \times 10^9$/L at inclusion.

The primary outcome was the efficacy of rituximab by comparing the overall response rate (partial + complete response) at 1 year in both groups. Complete response was defined as haemoglobin level ≥11 g/dL (women) or 12 g/dL (men) (measured on two different occasions 4-week apart) without: features of ongoing haemolysis, any ongoing treatment for warm AIHA or recent transfusion. Partial response was defined as haemoglobin level ≥ 10g/dL with at least a 2g increase from baseline (i.e. at diagnosis) without any treatment other than prednisone given at a daily dose <10 mg or recent transfusion.

At 1 year, with an intention to treat analysis, the overall response rate (complete and partial response) was 75% [47.6–92.7%] with rituximab versus 31% [11.0–58.7%] with placebo (P=0.032). At 2 years, 10/16 patients (63%) with rituximab versus 3/16 (19%) with placebo showed complete response (P=0.029).

Cold AIHA

Reynaud et al meta-analysis [6]

In the meta-analysis of the efficacy and safety of rituximab in AIHA described above (**Reynaud et al**), data taken from 6 studies (n=109) demonstrated an overall response rate to rituximab in cold antibody types of AIHA of 57% (CI95% 47; 66). The complete response rate was 21% (CI95% 6; 51 [7 studies, n=118]).

Other efficacy data:

Berentsen et al prospective study [9]

This single-arm prospective study was not included in the meta-analysis by **Reynaud et al**, as the study investigated overall response to combination therapy with rituximab and 40mg/m^2 body surface area of fludarabine. The study population consisted of 29 adult patients with chronic cold haemagglutinin disease and the presence of a clonal B-cell lymphoproliferation. Overall response was the sum of complete response (defined as absence of anaemia, no signs of haemolysis, disappearance of symptoms of cold haemagglutinin disease, undetectable monoclonal serum protein, and no signs of clonal lymphoproliferation) and partial response (defined as stable increase in haemoglobin concentration of ≥20 g/litre or to the normal range, combined with reduction of serum immunoglobulin M concentrations by ≥ 50% of the initial level or to the normal range, improvement of clinical symptoms and transfusion independence).

A total of 22/29 (76%) people had a response (complete or partial) to treatment, including 6/29 (21%) who experienced a complete response and 16/29 (55%) who had a partial response. The median duration of follow-up in people who responded to treatment during the study was 33 months (range 3 to 66 months). At this point, 5 people (23% of all responders, and 31% of partial responders) had relapsed, whilst 77% of responders remained in remission.

Summary of safety data:

In the RCT by **Birgens et al** there was no statistically significant difference between the prednisolone monotherapy and prednisolone plus rituximab groups in any adverse event in adults with warm AIHA. The most commonly reported adverse events for participants in the prednisolone monotherapy and prednisolone plus rituximab 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); several of which were probably related to prednisolone. There were 8 non-fatal serious adverse events in 5 people in the prednisolone plus rituximab group: pneumonia (3 events), fever (2 events), urinary tract infection (2 events) and *Clostridium difficile* enteritis (1 event). In the prednisolone monotherapy group there were 4 non-fatal serious adverse events in 4 people: pneumonia (2 events), urinary tract infection (1 event) and pulmonary embolism (1 event). There was 1 fatal serious adverse event (pneumonia) in the prednisolone plus rituximab group that was possibly treatment-related. [2]

For the meta-analysis **Reynaud et al** stated that nineteen studies reported 38 adverse events in 364 patients, and the overall adverse event rate was 14% (95% CI 9 - 21%). Sixteen events (42%) were infusion-linked side effects, mostly chills and fever. Twenty-two events (58%) were more severe: 4 neutropenias 18 severe infections, including 1 viral infection, and one Pneumocystis jiroveci pneumonia. Seventeen patients out of 364 (4.6%) died during follow-up. [6]

Michel et al stated that no immediate post-infusion reactions were reported in both rituximab and placebo groups. Two episodes of neutropenia were observed with rituximab. These two

episodes were transient and asymptomatic. Two cases of pneumonia occurred with rituximab. Ten severe adverse events concerning seven patients with mostly severe infections were reported with placebo, some fatal, and a massive pulmonary embolism occurred in one patient on day 15 of the study just before their second infusion. Within 24 months of follow-up, six patients with placebo died versus none with rituximab. [8]

The summary of product characteristics (SPC) for rituximab (MabThera) lists the following adverse events [1]:

System Organ Class	Very Common (>1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to < 1/1000)	Very Rare (<1/10,000)	Not known
Infections and infestations	bacterial infections, viral infections, bronchitis	sepsis, pneumonia, febrile infection, herpes zoster, respiratory tract infection, fungal infections, infections of unknown aetiology, acute bronchitis, sinusitis, hepatitis B		serious viral infection Pneumocystis jirovecii	PML	
Blood and lymphatic system disorders	neutropenia, leucopenia, febrile neutropenia, thrombo-cytopenia	anaemia, pancytopenia, granulocyto-penia	coagulation disorders, aplastic anaemia, haemolytic anaemia, lymphaden-opathy		transient increase in serum IgM levels	late neutropenia
Immune system disorders	infusion related reactions, angioedema	hypersensitivity		anaphylaxis	tumour lysis syndrome, cytokine release syndrome, serum sickness	infusion-related acute reversible thrombocyto-penia
Metabolism and nutrition disorders		hyperglycaemia, weight decrease, peripheral oedema, face oedema, increased LDH, hypocalcaemia				
Psychiatric disorders			depression, nervousness,			
Nervous system disorders		paraesthesia, hypoaesthesia, agitation, insomnia, vasodilatation, dizziness, anxiety	Dysgeusia		peripheral neuropathy, facial nerve palsy	cranial neuropathy, loss of other senses
Eye disorders		lacrimation disorder, conjunctivitis			severe vision loss	
Ear and labyrinth disorders		tinnitus, ear pain				hearing loss
Cardiac disorders		myocardial infarction, arrhythmia, atrial fibrillation, tachycardia, cardiac disorder	left ventricular failure, supra-ventricular tachycardia,ventricular tachycardia,angina,myocardial ischaemia, bradycardia	severe cardiac disorders	heart failure	
Vascular disorders		hypertension, orthostatic hypotension, hypotension			vasculitis (predominately cutaneous), leukocytoclastic vasculitis	
Respiratory, thoracic and mediastinal disorders		Bronchospasm, respiratory disease, chest pain, dyspnoea, increased cough, rhinitis	asthma, bronchiolitis obliterans, lung disorder, hypoxia	interstitial lung disease	respiratory failure	lung infiltration,
Gastrointestinal disorders	nausea	vomiting, diarrhoea, abdominal pain, dysphagia, stomatitis, constipation, dyspepsia, anorexia, throat irritation	abdominal enlargement		gastro-intestinal perforation	
Skin and subcutaneous tissue disorders	pruritus, rash, alopecia	urticaria, sweating, night sweats, skin disorder			severe bullous skin reactions, Stevens-Johnson syndrome toxic epidermal necrolysis (Lyell's syndrome)	

Musculoskeletal, connective tissue and bone disorders		hypertonia, myalgia, arthralgia, back pain, neck pain, pain				
Renal and urinary disorders					renal failure	
General disorders and administration site conditions	fever, chills, asthenia, headache	tumour pain, flushing, malaise, cold syndrome, fatigue, shivering, multi-organ failure	infusion site pain			
Investigations	decreased IgG levels					

Rituximab is contraindicated regardless of its indication for patients with hypersensitivity to the active substance or any product excipients, in active/severe infections and patients who are severely immunocompromised.

The SPC contains special warnings relating to infusion related reactions (listed as a very common adverse event); infections including potentially fatal progressive multifocal leukoencephalopathy, hepatitis B reactivation and the risk of concomitant use of live vaccines; severe and potentially fatal skin reactions such as Toxic Epidermal Necrolysis and Stevens-Johnson syndrome; cardiac disorders (myocardial infarction, angina pectoris, atrial fibrillation and heart failure); and haematological toxicities (late neutropenia).

According to the SPC there are limited data on possible drug interactions with rituximab. [1]

Strengths and limitations of the evidence:

Strengths

- An RCT conducted by **Birgens et al.** demonstrated that using a combination of prednisolone and rituximab as first-line therapy in patients with newly diagnosed warm AIHA leads to significantly higher response rates and longer relapse free survival than can be achieved by prednisolone monotherapy.
- **Michel et al** concluded that in warm AIHA, response to rituximab was significantly higher than the response to placebo. [8]
- A meta-analysis demonstrated an improvement in overall response for warm and cold type AIHA patients treated with rituximab. [6]
- Rituximab has been available as a licensed medicine in the UK since 1998 and has an extensive pool of safety data. [1]
- Adverse events associated with rituximab are generally mild to moderate in severity; with infusion-related reactions and infections the most frequently reported.
- Rituximab is recommended as 2nd line treatment option in warm AIHA and mixed AIHA by the British Society for Haematology (BSR). The BSR also recommend rituximab and combination rituximab/fludarabine as a 1st line treatment for cold haemagglutinin disease.
- The continued introduction of biosimilar preparations of rituximab may enable more cost-effective treatment regimens.
- Rituximab provides an alternative therapeutic option to splenectomy and cytotoxic drugs in patients unresponsive or contraindicated to steroids.
- Rituximab is usually given as a single course of treatment and is intended to induce long term remission of AIHA.

Limitations

- There is a lack of high quality double-blinded RCT data relating to the use of rituximab in AIHA, particularly in cold type AIHA

- The RCTs performed to date were conducted in a limited number of patients and used different doses of rituximab.
- The overall quality of reported studies is poor with varied study populations and a lack of standardised outcome measures.
- Although data from a meta-analysis demonstrated relatively high overall and complete response rates to rituximab, the data is mainly derived from observational studies and lacks comparison with placebo.
- Rituximab is **NOT licensed for use in AIHA** and has limited safety data for this indication.
- Patients would be required to attend hospital weekly for four weeks to be administered an intravenous infusion of rituximab over several hours.

Summary of evidence on cost effectiveness:

N/A

Prescribing and risk management issues:

Rituximab should be administered under the close supervision of an experienced healthcare professional, and in an environment where full resuscitation facilities are immediately available. Premedication consisting of an anti-pyretic and an antihistaminic, e.g. paracetamol and diphenhydramine should be given before each dose of rituximab. Patients should be given information relating to potential increased infection risk including progressive multifocal leukoencephalopathy. [1]

Commissioning considerations:

Comparative unit costs:

Drug (alternative treatments if corticosteroids/ thrombopoietin receptor agonists contraindicated or treatment failure)	**Example regimen**	**Pack cost**	**Cost per patient per course/ per year (ex VAT)**
Rituximab (MabThera®)	***For average adult body surface area of 1.86 m^2 the total 4-week dose = 2790mg***	***2x10ml (100mg) vial = £349.25 1x50ml (500mg) vial = £873.15***	***£4889.60 per course***
Rituximab (Truxima®/Rixathon®)	***For average adult body surface area of 1.86 m^2 the total 4-week dose = 2790mg***	***2x10ml (100mg) vial = £314.33 1x50ml (500mg) vial = £785.84***	***£4,400.68 per course***
Elective splenectomy	One-off treatment		**£3252 to £4548** [2]
Azathioprine	100-200mg daily [3]	56x50mg tabs = £2.20	**£28.68 to £57.36 per year**
Ciclosporin	Average adult (63kg) dose (5mg/kg/day) = 315mg daily [3]	30x100mg caps = £68.28 30x50mg caps = £35.97	**Approx. £2,623 per year**
Danazol	200mg three to four times daily [3]	28x100mg caps = £18.40 56x200mg = £66.20	**£1,295 to £1726 per year**

Drug (alternative treatments if corticosteroids/ thrombopoietin receptor agonists contraindicated or treatment failure)	Example regimen	Pack cost	Cost per patient per course/ per year (ex VAT)
Mycophenolate mofetil	500mg titrated up to 1000mg twice a day for three to four months [3]	100x250mg caps = £82.26 50x500mg tabs = £5.66	**Assuming titration approx. cost £35.67 to £48.35 per course**
Costs based on June 2018 MIMS list prices. Provider contract prices may vary. This table does not imply therapeutic equivalence of drugs or doses.			

Associated additional costs or available discounts:

The cost of rescue treatments following relapse and hospital admissions related to the different interventions may lead to additional costs however the level of additional cost for each intervention cannot be accurately estimated.

Provider trusts may be able to obtain rituximab at a discounted contract price (these prices are confidential).

Productivity, service delivery, implementation:

Adult AIHA is a rare condition with an incidence of approximately 1 per 100,000 population per year. [3] Patients would be required to attend specialist haematology services weekly for four weeks to be administered an intravenous infusion of rituximab over several hours.

Anticipated patient numbers and net budget impact:

According to Orphanet the prevalence of autoimmune haemolytic anaemia is 1-9 people per 100,000 population. [10]

Using an average estimate of prevalence of 4.5 people per 100,000 would equate to approximately 80 patients in the Lancashire and South Cumbria STP with AIHA. Not all patients with AIHA will require treatment, some patients will not be the commissioning responsibility of the CCGs and some patients may be already managed by other interventions.

If 20% (approximation) of AIHA were treated with rituximab this would represent 16 patients from the Lancashire and South Cumbria STP.

Using the MIMS listed price for biosimilar rituximab (Truxima®/Rixathon®) the total annual cost for one course of treatment would be:

16 x £4,400.68 = **£70,410**

For the same group of patients an alternative one-off intervention, an elective splenectomy would cost:

16 x £3252 to £4548 = **£52,032 to £72,768**

Excluding differences in relapse rates and associated costs, use of rituximab in place of elective splenectomy would therefore represent a maximum cost pressure of approximately £18,000 or a maximum cost saving of approximately £2,000.

Innovation, need, equity:

Rituximab intravenous infusion may be considered as an alternative treatment option in those patients whose condition is refractory to corticosteroid treatment.

Patients may need to travel to a specialist haematology service for four weekly infusions of rituximab. This may present accessibility issues particularly for those unable to travel due to age, disability or socioeconomic reasons.

References

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[8] M Michel et al, "A randomized and double-blind controlled trial evaluating the safety and efficacy of rituximab for warm auto-immune hemolytic anemia in adults (the RAIHA study)," *American Journal of Hematology,* vol. 92, pp. 23-27, 2017.

[9] S Berentsen et al, "High response rate and durable remissions following fludarabine and rituximab combination therapy for chronic cold agglutinin disease," *Blood,* vol. 116, pp. 3180-3184, 2010.

[10] Orphanet, "Autoimmune hemolytic anemia," [Online]. Available: https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Expert=98375&lng=EN. [Accessed 12 June 2018].

Grading of evidence (based on SORT criteria):

Levels	Criteria	Notes
Level 1	Patient-oriented evidence from: • high quality randomised controlled trials (RCTs) with low risk of bias • systematic reviews or meta-analyses of RCTs with consistent findings	High quality individual RCT= allocation concealed, blinding if possible, intention-to-treat analysis, adequate statistical power, adequate follow-up (greater than 80%)
Level 2	Patient-oriented evidence from: • clinical trials at moderate or high risk of bias • systematic reviews or meta-analyses of such clinical trials or with inconsistent findings • cohort studies • case-control studies	
Level 3	Disease-oriented evidence, or evidence from: • consensus guidelines • expert opinion • case series	Any trial with disease-oriented evidence is Level 3, irrespective of quality

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