HERTFORDSHIRE AND WEST ESSEX AREA PRESCRIBING COMMITTEE (APC)

RITUXIMAB (BIOSIMILAR) FOR THE TREATMENT OF AUTOIMMUNE HAEMOLYTIC ANAEMIA (AIHA) IN ADULTS.

RECOMMENDED FOR RESTRICTED PRESCRIBING (RED)

Name: generic	What it is	Indication	Decision last revised	Decision Status	NICE / SMC Guidance
Rituximab (biosimilar)	monoclonal antibody that targets CD20 surface antigen, expressed on normal & malignant B cells.	Treatment of autoimmune haemolytic anaemia (AIHA) in adults.	December 2017 HMMC May 2019 WEMOPB	Final	NICE & SMC - No Guidance

Rituximab (biosimilar) is RECOMMENDED for restricted use for the treatment of AIHA in adults as a second line treatment option alongside splenectomy, immunosuppressive drugs and IVIG (RED)

Initiation criteria:

- For secondary care specialist initiation and prescribing only
- 1st line treatment: steroids (prednisolone 1mg/kg/day, range 0.5-2mg/kg/day. Taper steroids if Hb>100g/l to 20-30mg OD by 4-6/52 then by 5mg reduction every 1/12)
- 2nd line treatment is indicated if there is a lack of steroid response within 3 weeks of starting course, relapse during or after steroid tapering:
  - Patients with haemolytic anaemia (Hb<100 g/l, refractory to steroid treatment), or
  - moderate/mild anaemia (Hb 100-110 g/l requiring at least 0.5 mg/kg of steroids for maintenance dosage) for more than three weeks.
- Rituximab is given by intravenous (IV) infusion at a dose of 375mg/m^2 body surface area weekly for 4 weeks.

Stopping Criteria:

- Hb >120g/l, no haemolysis features (not increased reticulocytes, LDH, bilirubin)

Where there is an adequate response, treatment may be repeated when required, no more frequently than 6 monthly.

Background Information

- Autoimmune haemolytic anaemia is a relatively rare condition caused by autoantibodies directed against a person's own red blood cells. The condition has warm and cold antibody types. Warm antibody type can be idiopathic or secondary to other conditions. Cold antibody types include cold haemagglutinin disease (CHAD) and paroxysmal cold haemoglobinuria
- Rituximab is a monoclonal antibody that targets the CD20 surface antigen, which is expressed on normal and malignant B cells. Rituximab binds to the CD20 surface antigen on B cells mediating cell lysis, and inducing cell death by apoptosis.
- Rituximab use for AIHA is off-label.

Assessment against Ethical Framework

Evidence of Clinical Effectiveness (see references for links to full evidence evaluations and guidelines)

- **A NICE Evidence Summary has summarised the most significant evidence for the use of rituximab for AIHA.** Although there is limited high-quality evidence (only 1 RCT so largest uncontrolled studies included) there is some evidence of effectiveness and the summary is as follows:
  - Limited high-quality evidence was identified that investigated how well rituximab works for treating AIHA. One RCT suggested that after 12 months, prednisolone plus rituximab 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 rituximab in warm and cold autoimmune haemolytic anaemia, but limitations of these studies make it difficult to draw any firm conclusions.
    - An open label RCT (Birgens et al. 2013) (randomisation process not described) in 64 adults with newly diagnosed and previously untreated warm autoimmune haemolytic anaemia suggested that after 12 months, prednisolone plus rituximab 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).

Study had low patient numbers and included primary autoimmune haemolytic anaemia, concomitant autoimmune disease, or low-grade B-cell lymphoproliferative neoplasia.

- Uncontrolled studies (Dierickx et al. 2009; Maung et al. 2013; Barcellini et al. 2013 and Zecca et al. 2003) in people

with warm autoimmune haemolytic anaemia (4 studies; n=101 in total) reported complete response rates ranging from 27% to 67%.
  - Uncontrolled studies (Berentsen et al. 2004; Berentsen et al. 2006; Berentsen et al. 2010; Schollkopf et al. 2006 and Barcellini et al. 2013) in people with cold haemagglutinin disease (5 studies; n=142 in total) reported complete response rates ranging from 4% to 54%.

The uncontrolled studies included small numbers of participants with different disease presentation, concomitant treatment and did not compare rituximab with any other treatment. There was no standardised definition of response and these varied.

- **The British Society for Haematology has recently published guidelines on the diagnosis and management of primary autoimmune haemolytic anaemia** (including rituximab). This appears to reflect the limitations in the evidence base for the treatment of AIHA. In summary (with evidence grade: Strength of Recommendation - 1 = strong, 2 = weak; Quality of Evidence – A = high, B = moderate, C = low, D = very low)
  - **Warm AIHA**
    - Rescue therapy - Consider IVIg or plasma exchange for severe or life threatening anaemia (2C)
    - First line therapy - prednisolone 1 mg/kg/day (1B)
    - Second line therapy should be considered if (2C):
      - No response to 1 mg/kg/day after 3 weeks
      - Relapse during or after steroid reduction
    - Second line treatment: The best-studied and most efficacious treatments used are rituximab and splenectomy. Approximately 70% of cases respond to splenectomy but even higher response rates are reported with rituximab. Following splenectomy, refractory or relapsing patients often require immunosuppression and the rate of serious infection appears higher post-splenectomy (Rivero et al, 1979; Barcellini et al, 2014; Roumier et al, 2014). Given the significance of infection and chronic course of AIHA, most patients will benefit from an effective well-tolerated steroid-sparing agent prior to consideration of splenectomy.
    - Second line treatment - Rituximab (1B)
    - Third line treatment: Azathioprine, ciclosporin, danazol, mycophenolate mofetil, splenectomy (2C)
  - **Primary CHAD**
    - Consider plasma exchange or steroids for severe or life-threatening anaemia (2C)
    - Patients should be advised to avoid cold exposure where possible (1C)
    - Indications for treatment: symptomatic anaemia, severe circulatory symptoms or transfusion dependence (1C)
    - First line treatment: rituximab, or if clonality has been demonstrated, the addition of fludarabine may be considered (1B)
    - Note the guideline states the following for alternative treatment options:
      - Splenectomy: Evidence of efficacy is lacking and splenectomy appears to have a very limited role.
      - Pharmacological treatment: CHAD is less responsive than warm AIHA. Case reports or small series do not encourage the use of chlorambucil, cladribine, azathioprine or cyclophosphamide.

- The NICE Evidence Summary references a **Review Publication (Zanella and Barcellini 2014). from Haematologica (The Journal of the European Haematology Association) on Treatment of autoimmune hemolytic anemias (2014)** and summarises that:
  - 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.

Rituximab Safety

- The reported adverse events from the studies reported in the NICE Evidence summary appear consistent with the known adverse events associated with rituximab eg infusion reactions and infections
- Infusion related reactions are very common.
- Serious infections, including fatalities, can occur during rituximab therapy. It is contraindicated in people with an active, severe infection, and in severely immunocompromised.
- Very rare cases of fatal progressive multifocal leukoencephalopathy have been reported

Cost of treatment and Cost Effectiveness

- The NICE evidence summary states that comparing the cost of rituximab with other therapies for autoimmune haemolytic anaemia is difficult because there is a lack of evidence to confirm the optimal dose, guide the use of recurrent courses in refractory cases, and confirm the advice on other aspects of the clinical pathway such as combination with other treatments.
- Most studies in the NICE evidence summary used intravenous rituximab at a dosage of 375 mg/m^2 body surface area weekly for 4 weeks. One study used a lower fixed dose of rituximab 100 mg weekly for 4 weeks.

- The NICE evidence summary for ITP states the cost to commissioners of an elective splenectomy as estimated to be in the range of £3252 to £4548, depending on the complexity of the procedure. However, local specialists have indicated that costs may be higher as this is a high risk procedure.
- 1 course of rituximab (including drug and administration costs) is similar or lower cost than splenectomy, lower cost than IVIG but higher cost than immunosuppressants. Patients may require repeat courses no more frequently than 6 monthly.
- No cost-effectiveness analysis available

The needs of the population

- The needs of the population appear high as there appear to be limited evidence based treatment options. ENHT specialists have stated that current treatments given for AIHA are steroids, for first line, and then IVIG, splenectomy, immunosuppressants: azathioprine, mycophenolate and cyclosporin. There are no strict pathways for second line treatment.
- ENHT specialists have stated that patients who currently could not receive rituximab, were occasionally referred to other Trusts, as their anaemia was very difficult to be controlled, with various treatment options. They required intermittently red blood cell transfusions and hospital admissions.
- Patients may prefer an IV treatment rather than splenectomy to avoid surgery (including that surgery may not be effective) and the risks of surgery and longer term safety concerns after splenectomy including the subsequent increased risk of infection and need for prophylactic antibiotics.
- Patients may prefer an IV treatment rather than taking daily oral immunosuppresants.

The needs of the community

- The number of patients requiring treatment with rituximab would appear to be relatively low (approximately a maximum of six to eight patients with primary AIHA and four to five with secondary AIHA per CCG of 600,000 population per year), which would cost approximately £23-57k (drug costs: £3k-31k; administration costs: £20k-26k).
- The overall cost impact of the approval of rituximab for AIHA appears uncertain. Some patients treated with rituximab may avoid the costs of steroids, immunosuppresants and splenectomy.
- The overall longer term costs and outcomes for patients treated with rituximab, splenectomy or immunosuppresants appear uncertain.
- There are obviously associated activity costs for patients with severe anaemia requiring hospitalisation and treatment with red blood cell transfusions and rescue therapy including IVIG which may be avoided if rituximab treatment is effective.
- IVIG is high cost with restrictions on supply and specialists have indicated should be reserved for emergency rescue therapy only. IVIG is the commissioning and funding responsibility of NHS England so the overall health economy would benefit from any reduced use but not CCGs specifically.

Policy Drivers

- There are no NICE guidelines or local pathways for the treatment of AIHA including recommendations for rituximab
- As reported above there is a NICE evidence summary from 2015 which summarises the evidence for rituximab for AIHA
- DoH Clinical Guidelines for Immunoglobulin use - Autoimmune haemolytic (blue indication) – recommended for symptomatic or severe anaemia (Hb <6 g/dL, except patients with co-morbidities) or thrombocytopenia (Evans syndrome platelets <20x10^9/L) refractory to conventional therapy with corticosteroids (or steroids contra-indicated); OR Temporising measure prior to splenectomy
- As reported above the British Society for Haematology has recently published guidelines on the diagnosis and management of primary autoimmune haemolytic anaemia (including rituximab)
- Cambridgeshire and Peterborough CCG have approved rituximab for AIHA: Warm AIHA – disease has NOT responded to corticosteroids; Cold AIHA - patient is symptomatic and has significant haemolysis
- North Central London Joint Formulary committee – recommend rituximab for restricted use for AIHA: warm-AIHA – 2nd line option after prednisolone; Cold-AIHA – 1st line option
- WECCG, Bedfordshire and Luton CCGs, Aylesbury Vale CCG, Chiltern CCG and Mid Essex CCG appear to have not considered rituximab for AIHA.

Equity

- No impact anticipated

Implementability

- No issues identified although ENHT have indicated that there may be internal Trust capacity issues associated with rituximab administration that may need to be addressed if increased use.

References

- NICE Evidence summary [ESUOM39]: Autoimmune haemolytic anaemia: rituximab (February 2015) https://www.nice.org.uk/advice/esuom39/chapter/Key-points-from-the-evidence
- Hill Q et al. on behalf of the British Society of Haematology (2017) The diagnosis and management of primary autoimmune haemolytic anaemia. British Journal of Haematology, 2017, 176, 395-411 http://onlinelibrary.wiley.com/doi/10.1111/bjh.14478/full
  Hill Q et al. on behalf of the British Society of Haematology (2017) Guidelines on the management of drug-induced immune and secondary autoimmune, haemolytic anaemia. British Journal of Haematology, 2017, 177, Issue 2, 208–220 http://onlinelibrary.wiley.com/doi/10.1111/bjh.14654/full

Version	2.0 Harmonisation of Hertfordshire Medicines Management Committee (HMMC) guidance and West Essex Medicines Optimisation Programme Board (WEMOPB) guidance updates include: • Rebadging with HWE ICB and removal of ENHCCG and HVCCG headers • Review date removed and replaced with standard statement.
Developed by	ENHCCG and HVCCG PMOT teams with specialists from WHHT and ENHT
Approved by	HMMC and WEMOPB
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Review date:	The recommendation is based upon the evidence available at the time of publication. This recommendation will be reviewed upon request in the light of new evidence becoming available.
Superseded version	1.0