HIGH COST DRUGS SUBGROUP

GMMMG Greater Manchester Medicines Management Group

NHS

January 2018

# Rituximab for Treatment of Refractory Primary Idiopathic Immune Cytopenias

**The High Cost Drugs Subgroup discussed the above at its meeting on 24th January 2018. The recommendation of this subgroup is as follows:**

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| **Recommendation** | Rituximab is recommended as a treatment option for adult patients with **Refractory Idiopathic Thrombocytopenia Purpura (ITP), Autoimmune Haemolytic Anaemia (AIHA) or Evans syndrome where:**<br><br>• There is failure to respond to or a contraindication to standard active treatments and rescue therapies (as appropriate to the type of immune cytopenia) or severe disease requiring frequent courses of rescue therapies **and**<br><br>• In the case of ITP, the NICE approved interventions (Eltrompopag TA 293 and romiplostim TA 221) are contraindicated otherwise considered inappropriate.<br><br>n.b. Rituximab is not suitable for acute emergency treatment. |
| **Background** | **Immune cytopenias** are characterised by the production of antibodies against blood cells. Despite being well-recognized, they present a therapeutic dilemma because of differences in subtypes, associated diseases and individual patient presentation.<br><br>The immune cytopenias covered by this commissioning statement include;<br><br>**Refractory Idiopathic Thrombocytopenic Purpura (ITP):** This is characterised by isolated thrombocytopenia (platelet <100 x $10^9$/L) in the absence of any underlying cause. It generally follows a chronic course. Treatment is indicated with very low platelet counts (<30 x $10^9$/L), or significant bleeding. The goal is to achieve a platelet count associated with adequate haemostasis.<br><br>**Refractory Autoimmune Haemolytic Anaemia (AIHA):** This is a decompensated acquired haemolysis caused by the immune system acting against its own red blood cells. The condition can be subdivided based on serology into warm type (65%), cold type (29%) also known as CHAD (cold haemolytic autoimmune disorder) and mixed type i.e. warm & cold (5%). Treatment differs slightly for each and further information is available in the British Journal of Haematology. There is also a further subtype known as paroxysmal cold haemoglobinuria which is not covered by this commissioning position statement.<br><br>**Evans syndrome:** This is a rare condition which is characterised by ITP and AIHA occurring in the same patient (either simultaneously or sequentially). It is generally chronic and neutropenia is also a common feature.<br><br>**Treatment.** There isn't a completely validated and standard therapeutic approach to treatment of the above conditions because randomised clinical trials are difficult to |

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| | implement. However, depending on the subtype patients are generally treated with corticosteroids and in severe cases immunoglobulins initially. The majority of patients will respond to these but a proportion will either relapse or not respond and require alternative therapy. Patients who do not respond to treatment are at risk of life threatening bleeding or anemia.<br><br>Treatments options for refractory patients include splenectomy or off-label treatment with cytotoxic immunosuppressive agents. Rituximab represents an alternative but the precise place in therapy in relation to other second line therapies has not been defined due to limited published research and case reports. The decision around this will need to be taken locally by providers or clinical teams with consideration of individual patient factors. |
| **Efficacy and Safety** | Rituximab has been available as a licensed medicine in the UK since 1998 and the overall safety and tolerability has been well described. It is NOT licensed for use in immune cytopenias and safety data for these indications is poorly reported.<br><br>Adverse events associated with rituximab are generally mild to moderate in severity; with infusion-related reactions and infections the most frequently reported.<br>Cases of hepatitis B reactivation have been reported in people receiving rituximab and Hepatitis B screening should be performed before starting treatment.<br><br>**ITP:** Limited data as outlined by NICE suggests that when rituximab is used to treat ITP it can induce a response in up to 63% of adults with complete responses seen in up to 44% of patients.<br><br>**AIHA:** Reported response rates vary considerably and the long term remission rate is unknown. NICE have produced an evidence summary for AIHA and use is also supported by the British Committee for Standards in Haematology<br><br>**Evans Syndrome:** The estimated prevalence of Evans syndrome is 1in 1,000,000. As a consequence there is limited published data around efficacy of rituximab in this condition. But there is a biologic plausibility to use given that it is used to treat both ITP and AIHA when they occur in isolation. |
| **Cost Effectiveness/ Affordability** | There are no published cost effectiveness studies for use of rituximab in the listed indications; but it is estimated that less than 40 patients per year across Greater Manchester will require treatment with rituximab in line with these recommendations which would equate to less than £224,000.<br>Using an average adult body surface area of 1.86$m^2$ the cost per four week course at a 375mg/$m^2$* dose would be £5600 per patient. (MIMS Jan 2018 - CMU contract prices may differ).<br><br>**Commissioning Arrangements:** Rituximab is a high cost PbR excluded drug.<br>**CCGs** are the responsible commissioner when it is used to treat the above immune mediated cytopenias in adults.<br>**NHS England** is the responsible commissioner for rituximab when used in children or when used to treat ITP associated with Primary Immune Deficiency (PID) or other immune deficiencies such as cancer. Further information can be found in the NHS England Manual for Prescribed Specialist Services.<br><br>*a range of doses have been quoted in the literature but the majority of published evidence relates to 375mg/$m^2$ |
| **Monitoring** | Where Blueteq has been introduced to the trust as part of the contractual arrangements, a form should be completed and funding approval will be made by meeting the criteria outlined on completion and submission of a Blueteq form. |

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| | Given the limited nature of the evidence for clinical and cost-effectiveness, it is recommended that use is monitored to inform future review and decision making, as such providers may be asked to submit outcomes and usage data. |
| **Patient perspective** | Rituximab is administered as an infusion over several hours and is usually given as a 4-week course with the aim of inducing a long-term response, whereas some other treatments might need to be taken continuously. Other treatment options include splenectomy, which some people may prefer to avoid.<br><br>Routine commissioning for the outlined indications will mean that patients can access an accepted treatment in a timely manner without the requirement for an individual funding request and will ensure equitable access to this treatment across Greater Manchester. |

**References available on request**

**Appendix 1.**

**Table 1:** Estimated Patient numbers requiring treatment with Rituximab for Auto Immune Haemolytic Anaemia

| | **Auto Immune Haemolytic Anaemia – Estimated Patient Numbers** [i] | | |
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| **Incidence** | The reported Incidence of AIHA is 1 per 100,000 of the population of which 50% have primary idiopathic presentations.<br><br>It is known that the incidence of AIHA increases with age, but for the purposes of this evaluation it is assumed that there is an incidence of primary AHIA of 0.5 people per 100,000 of the adult population. | | |
| **Expected number of adult patients across GM with primary AIHA (based on an adult population of 2.6 million)** | 0.5 per 100,000 equates to 13 adults patients across GM of which it is estimated that<br><br>65% or 8-9 people will have warm type<br>29% or 3-4 people will have cold type<br>5% will have mixed type or 0.65 persons in a population of 2.6 million<br>1% will have paroxysmal or 0.13 per 2.6 million | | |
| **Expected response rate to 1st line emergency treatments (based on available published data)** | **Warm AIHA**<br>Published response rates suggest that 2/3 or 6 patients across GM will respond to steroids and 1/3 will be refractory<br><br>Of the steroid responders 20% (1-2 pts) are expected to remain in remission and 80% (4-5pts) relapse or require longer term steroid treatment to maintain homeostasis and therefore should be considered for second line treatments. | **Cold AIHA**<br>Not applicable, cold AIHA is less responsive to steroids, splenectomy and conventional immunosuppressants and guidance BSH recommends that rituximab as 1st line treatment | **Mixed AIHA**<br>Steroid responsive but most patients go on to have chronic haemolysis and require second line treatments |
| **Expected numbers of refractory patients and proportion likely to be treated with rituximab** | 7-8 of the 9 patients treated with steroids will likely need second line treatments with rituximab or other immunosuppressant agent | 3-4 patients | 0-1 patients |
| **Published initial rituximab response rate** | 70-100% response rate.<br><br>Better outcomes are seen with a shorter duration of AHIA , rituximab response is not affected by splenectomy<br><br>This would mean that if 8 patients are treated with rituximab in GM 5-8 patients are expected to respond | Primary response at 4 weeks = 51% i.e. if 4 patients in GM are treated 2 are expected to respond | |
| **Sustained rituximab response rate** | The long term remission rate is unknown but a relapse rate of 14–25% after a median of 15–21 months and 50% after 30 months has been reported<br><br>i.e. at 21 months it is estimated that 4-6 patients will have a sustained response which is maintained at 30months for 3-4 patients.<br><br>For those patients who relapse rescue treatment +/- a repeat course of rituximab or alternative second line therapy may be required | 57–89% relapse after 6·5–11 months | |
| **Summary of estimated GM** | Warm AIHA -8 patients | | |

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| **impact** | Cold ITP -4 patients<br>Mixed AIHA -1 patient<br>Evans syndrome – unlikely to have any patients due to rarity of the condition |

**Table 2:** Estimated number of people eligible for rituximab to treat ITP[ii]

| | **% of people** | **Number of people across GM, based on an adult patient population of 2.6 million** |
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| Number of people who have ITP (UK prevalence) | **0.05%** | **1300** |
| Number of people who require treatment | **60%** | **780** |
| Number of people in whom first-line treatment is unsuccessful | **67%** | **522.6** |
| Number of people who require long-term treatment | **40%** | **209**<br>n.b. These patients would potentially be eligible for treatment with rituximab |
| Based on feedback from local specialists it is expected that only a proportion of patients would actually be treated with rituximab. Estimated at approximately 25 per year across GM.<br><br>N.b. The choice of second line treatment is based on individual patient factors and co-morbidities and there is no clear consensus regarding best practice.<br><br>In practice rituximab is often used prior to treatment with eltrombopag and romiplostim which are licensed for use in ITP. The product licence for the TPOs (thrombopoetin receptor agonists) states they should be used in patients who are refractory to other treatments (or as a second line treatment in patients who cannot have a splenectomy). The cost effectiveness model submitted for the NICE TA for eltrombopag states that it was assumed that patients had already been treated with rituximab where eligible and recommends that TPOs are used in patients who are refractory to other treatments.<br><br>Local experts have stated that maintenance of response varies but it is usually 1-2 years and repeat doses may be considered if the relapse occurs after at least 1 year. | | |

[i] British Journal of Haematology
[ii] NICE Costing Statement for Eltrombopag