MANAGEMENT IN CONFIDENCE

CLINICAL PRIORITIES ADVISORY GROUP
03 June 2020

Agenda Item No	2.2
National Programme	Blood and Infection
Clinical Reference Group	Haemoglobinopathy
URN	1821

Title
Rituximab and eculizumab for the prevention and management of delayed haemolytic transfusion reactions and hyperhaemolysis in patients with haemoglobinopathies.

Actions Requested	1. Support the adoption of the policy proposition
	2. Recommend its approval as an IYSD

Proposition
Routinely Commissioned This is a clinical commissioning policy proposition for the use of rituximab for the prevention and management and eculizumab for management of delayed haemolytic transfusion reactions (DHTR) and hyperhaemolysis (HH) in patients with haemoglobinopathies. Rituximab will be commissioned for adult and post-pubescent patients whilst eculizumab will be commissioned for patients of all ages in line with licensing restrictions of the drug to treat DHTR and HH patients. DHTR and HH are rare, life threatening complications of blood transfusion associated with red cell alloantibody formation and activation of complement. They are more typically seen in patients with haemoglobinopathies – sickle cell disease and thalassaemia - who may have undergone multiple blood transfusions over their lifetime. Current treatments consist of supportive care with products to stimulate new red cell production (erythropoietin) and treatments such as steroids and intravenous immunoglobulin (IVIg) to reduce the immune system breaking down red blood cells.

Rituximab has been used both to prevent the occurrence of DHTR in high risk patients and to manage severe ongoing DHTR/HH and eculizumab has been used to manage severe ongoing DHTR/ HH in patients at high risk of death and organ damage.

Clinical Panel recommendation
The Clinical Panel recommended that the policy progress as a routine commissioning policy.

The committee is asked to receive the following assurance:	
1.	The Head of Clinical Effectiveness confirms the proposal has completed the appropriate sequence of governance steps and includes an: Evidence Review; Clinical Panel Report.
2.	The Head of Acute Programmes confirms the proposal is supported by an: Impact Assessment; Engagement Report; Consultation Report; Equality and Health Impact Assessment Report; Clinical Policy Proposition. The relevant National Programme of Care has approved these reports.
3.	The Director of Finance (Specialised Commissioning) confirms that the impact assessment has reasonably estimated a) the incremental cost and b) the budget impact of the proposal.
4.	The Clinical Programmes Director (Specialised Commissioning) confirms that the service and operational impacts have been completed.

The following documents are included (others available on request):	
1.	Clinical Policy Proposition
2.	Engagement Report
3.	Evidence Summary
4.	Clinical Panel Report
5.	Equality and Health Inequalities Impact Assessment

No	*Metric*	*Summary from evidence review*
1.	Survival	Survival in the context of the publications is the number of patients treated with rituximab that survived elective procedures where there was a risk of DHTR/HH. All eight patients described by the four publications reporting this outcome survived. The publication with the strongest evidence was Noizat-Pirenne et al (2015) where the five patients described all survived however this evidence was indirect as no information on if patients had experienced prior DHTR/HH despite treatment with steroids or IVIg was

		available and all patients received matched blood for their elective transfusions. A high overall survival rate is important to clinicians, patients and their families. However, this study does not demonstrate that overall survival is improved by the intervention as limited conclusions can be drawn from a small case series. Since the study does not include a comparator, it is not possible to compare the outcomes for these patients with those receiving alternative treatments. The patients were not followed up at specified time intervals following the intervention so long-term survival is not considered.
2.	Progression free survival	/
3.	Mobility	/
4.	Self-care	/
5.	Usual activities	/
6.	Pain	/
7.	Anxiety / Depression	/
8.	Replacement of more toxic treatment	/
9.	Dependency on care giver / supporting independence	/
10.	Safety	Adverse events were not specifically measured but no adverse events were reported in the papers.
11.	Delivery of intervention	/

No	Metric	Summary from evidence review
1.	Acute health events- pain, stroke, Acute Coronary Syndrome	The publication of the four identified with the strongest evidence was Noizat-Pirenne et al (2015) where one of the five patients described experienced an acute health event-haemoglobinuria however this evidence was indirect as no information on if the patient had experienced prior DHTR/HH despite treatment with steroids or IVIg was available and they received matched blood for their elective transfusion. Low rates of acute health event reactions are important to clinicians, patients and their families. However, this study

		does not demonstrate definitively that the risk of acute health events is improved by the intervention as limited conclusions can be drawn from a small case series. Of the five patients described, only one suffered this type of complication which indicates there is very limited evidence that rituximab prevented further acute health events. Since the study does not include a comparator, it is not possible to compare the outcomes for these patients with those receiving alternative treatments.
2.	Acute health events- Acute facility utilisation	Acute facility utilisation in the context of the publications is the amount of additional time spent in an acute setting following an elective procedure where patients were treated with rituximab. Only one publication presented this information, Cattoni et al (2013), where the patient described experienced a DHTR/HH reaction seven days after their elective procedure. The patient was discharged after four weeks however it was not clear what the original intended length of stay was though this provides very limited evidence that acute facility utilisation is still possible despite treatment. The evidence presented was indirect as no information was included on if the individual was treated previously with steroids and IVIg pre-transfusion to no effect. A reduced rate of acute hospital usage is important to clinicians, patients and their families. However, this study does not demonstrate the intervention prevents acute facility utilisation as there are high levels of uncertainty when drawing wider conclusions from a case study. Since the study does not include a comparator, it is not possible to compare the outcomes for this patient with those receiving alternative treatments.
3.	Prevention of further haemolytic transfusion reaction	Prevention of further haemolytic transfusion reaction in the context of the publications is the number of patients who experienced a DHTR/HH following treatment with rituximab during their post-operative follow up care. Four of a total of eight patients experienced a DHTR/HH reaction, the publication with the strongest evidence was Noizat-Pirenne et al (2015) where three of the five patients described experienced a mild DHTR reaction. This evidence was indirect as no information was included on if patients had experienced prior DHTR/HH despite treatment with steroids or IVIG was available and all patients received matched blood for their elective transfusions. Prevention of further haemolytic transfusion reaction is important to clinicians, patients and their families. However,

		this study does not demonstrate that prevention of further haemolytic transfusion reaction is improved by the intervention as limited conclusions can be drawn from a small case series. Since the study does not include a comparator, it is not possible to compare the outcomes for these patients with those receiving alternative treatments.
4.	Requirement for further transfusion	Reducing the requirement for further transfusion in the context of the publications is the number of patients who required additional unplanned blood units following their elective follow up care. Two out of a total of three patients required further transfusions, the publication with the strongest evidence was Cattoni et al (2013) where the patient described required a further transfusion due to a DHTR/HH reaction to prevent severe anaemia. The evidence presented was indirect as no information was included on if the individual was treated previously with steroids and IVIg pre-transfusion to no effect. Reducing the requirement for further transfusion is important to clinicians. However, this study does not demonstrate that the intervention reduces the requirement for further transfusion as there are high levels of uncertainty when drawing wider conclusions from a case study. Since the study does not include a comparator, it is not possible to compare the outcomes for this patient with those receiving alternative treatments.
5.	Prevention of new alloantibody formation	Prevention of new alloantibody formation in the context of the publications is the number of patients treated with rituximab that had new alloantibodies in their blood at post-operative follow up. All seven patients described by the publications survived, the publication with the strongest evidence was Noizat-Pirenne et al (2015) where none of the five patients described had formed new alloantibodies between 3 months and 1 year post initial intervention. This evidence was indirect as no information was included on if patients had experienced prior DHTR/HH despite treatment with steroids or IVIg was available and all patients received matched blood for their elective transfusions. Prevention of new alloantibody formation is important to clinicians, patients and their families. However, this study does not demonstrate definitively that new alloantibody formation is prevented by the intervention although as no patients developed new antibodies there is limited evidence to suggest this is the case. Limited conclusions can be drawn from a small case series and since the study does not include

		a comparator, it is not possible to compare the outcomes for these patients with those receiving alternative treatments.

Use of eculizumab as treatment for the treatment of DHTR/HH

No	*Outcome measures*	*Summary from evidence review*
1.	Survival	Survival in the context of the publications is the number of patients treated with eculizumab that survived an episode of DHTR/HH. The only patient described by the publication survived. This evidence is indirect as the haemolytic reaction occurred >28 days post transfusion and initial treatment was with steroids, erythropoietin and cyclosporine, not IVIg and steroids. A high overall survival rate is important to clinicians, patients and their families. However, this study does not demonstrate that overall survival is improved by the intervention as limited conclusions can be drawn from a small case study. Since the study does not include a comparator, it is not possible to compare the outcomes for this patient with those receiving alternative treatments. The patient was not followed up at specified time intervals following the intervention so long-term survival is not considered.
2.	Progression free survival	/
3.	Mobility	/
4.	Self-care	/
5.	Usual activities	/
6.	Pain	/
7.	Anxiety / Depression	/
8.	Replacement of more toxic treatment	/
9.	Dependency on care giver / supporting independence	/
10.	Safety	/
11.	Delivery of intervention	/

No	Outcome measure	Summary from evidence review
1.	Acute health events-pain, stroke, ACS	The patient described by the publication went on to suffer splenic sequestration. This evidence is indirect as the haemolytic reaction occurred >28 days post transfusion and initial treatment was with steroids, erythropoietin and cyclosporine, not IVIg and steroids. Low rates of acute health event reactions are important to clinicians, patients and their families. However, this study does not demonstrate definitively that the risk of acute health events is improved by the intervention as limited conclusions can be drawn from a small case study. In the patient described, treatment with eculizumab and IVIG did not stop the haemolytic reaction and the patient went on to experience splenic sequestration and receive a splenectomy. Since the study does not include a comparator, it is not possible to compare the outcomes for these patients with those receiving alternative treatments.
2.	Prevention of new alloantibody formation	Prevention of new alloantibody formation in the context of the publications is the number of patients treated with eculizumab that had new alloantibodies in their blood at post-operative follow up. The publication reports that the patient developed several clinically significant alloantibodies though at what point during their inpatient episode this was identified was not clear. This evidence is indirect as the haemolytic reaction occurred >28 days post transfusion and initial treatment was with steroids, erythropoietin and cyclosporine, not IVIg and steroids. Prevention of new alloantibody formation is important to clinicians, patients and their families. However, this study does not demonstrate definitively that new alloantibody formation is prevented by the intervention the included patient was reported to have developed new antibodies. Limited conclusions can be drawn from a small case study and since the study does not include a comparator, it is not possible to compare the outcomes for these patients with those receiving alternative treatments.
3.	Stabilisation of haemoglobin/cessation of haemolysis	Stabilisation of haemoglobin/cessation of haemolysis in the context of the publications is the return of Hb levels to pre-DHTR levels following a DHTR/HH episode.

		Following splenectomy, the patient's haemoglobin levels stabilised. The publication does not detail the temporal relationship between eculizumab administration and haemoglobin levels. This evidence is also indirect as the haemolytic reaction occurred >28 days post transfusion and initial treatment was with steroids, erythropoietin and cyclosporine, not IVIg and steroids. Stabilisation of haemoglobin/cessation of haemolysis is important to clinicians, patients and their families. However, this study does not demonstrate that stabilisation of haemoglobin/cessation of haemolysis is reached by the intervention as there are high levels of uncertainty when drawing wider conclusions from a case study. Since the study does not include a comparator, it is not possible to compare the outcomes for these patients with those receiving alternative treatments.
4.	Requirement for further transfusion	Requirement for further transfusion in the context of the publications is the number of patients treated with eculizumab as a 2nd line treatment that required additional units of blood following treatment. The patient received another transfusion following eculizumab administration in advance of their splenectomy operation. This evidence is indirect as the haemolytic reaction occurred >28 days post transfusion and initial treatment was with steroids, erythropoietin and cyclosporine, not IVIg and steroids. This study does not demonstrate requirement for further transfusion is impacted by the intervention as there are high levels of uncertainty when drawing wider conclusions from a case study. Since the study does not include a comparator, it is not possible to compare the outcomes for these patients with those receiving alternative treatments.

Use of rituximab treatment of DHTR/HH

No	*Outcome measures*	*Summary from evidence review*
1.	Survival	Survival in the context of the publications is the number of patients treated with rituximab that survived a DHTR/HH episode.

		None of the patients included fully met the PICO. All the studies dealt with individual patients and did not follow up patients at specified time intervals following the reaction. None of the papers can be described as having stronger evidence than the other included papers as they were all individual case studies. A high overall survival rate is important to clinicians, patients and their families. However, none of the studies demonstrate that overall survival is improved by the intervention as there are high levels of uncertainty when drawing wider conclusions from case studies. Since the studies do not include a comparator, it is not possible to compare the outcomes for these patients with those receiving alternative treatments.
2.	Progression free survival	/
3.	Mobility	/
4.	Self-care	/
5.	Usual activities	/
6.	Pain	/
7.	Anxiety / Depression	/
8.	Replacement of more toxic treatment	/
9.	Dependency on care giver / supporting independence	/
10.	Safety	The only publication that described a treatment complication was Hannema et al (2010). A 1 ½ year-old patient was treated with rituximab and then experienced anaphylaxis at which point rituximab was discontinued. Rituximab was later reinitiated alongside increasing their dose of corticosteroids and was tolerated indicating the allergic reaction was not permanent. However, this study does not demonstrate that treatment complications are likely as there are high levels of uncertainty when drawing wider conclusions from a case study and the included patient did not have persistent reactions to rituximab. Since the study does not include a comparator, it is not possible to compare the outcomes for these patients with those receiving alternative treatments.

11.	Delivery of intervention	/

No	Outcome measure	Summary from evidence review
1.	Acute health events- pain, stroke, ACS	The publication with the strongest evidence was Chonat et al (2018) where the patient was treated with both drugs of interest identified in the PICO although order of administration of corticosteroids, IVIg, rituximab and eculizumab was not as specified by the PICO. The patient experienced pain altered mental status, and development of new diffuse pulmonary oedema the day after initiation of rituximab treatment and then went on to be given eculizumab after which the patient improved. Low rates of acute health event reactions are important to clinicians, patients and their families. However, this study does not demonstrate definitively that the risk of acute health events is improved by the intervention as limited conclusions can be drawn from a small case study. There is very limited evidence that rituximab prevented further acute health events although the evidence may suggest it ameliorated adverse health effects in conjunction with eculizumab. Since the study does not include a comparator, it is not possible to compare the outcomes for these patients with those receiving alternative treatments.
2.	Acute health events- Acute facility utilisation	None of the patients included fully met the PICO. None of the papers can be described as having stronger evidence than the other included papers as they were all individual case studies. The patients were admitted to hospital at the beginning of their episode of care. Information was not available on total length of stay or how complications experienced affected the length of time admitted. A reduced rate of acute hospital usage is important to clinicians, patients and their families. However, these

		studies do not demonstrate the intervention prevents acute facility utilisation as there are high levels of uncertainty when drawing wider conclusions from case studies. Since the studies do not include a comparator, it is not possible to compare the outcomes for this patient with those receiving alternative treatments.
3.	Prevention of new alloantibody formation	Prevention of new alloantibody formation in the context of the publications is the number of patients treated with rituximab that had new alloantibodies in their blood during their episode of care. The publication with the strongest evidence was Chonat et al (2018) where the patient was treated with both drugs of interest identified in the PICO although order of administration of corticosteroids, IVIG, rituximab and eculizumab was not as specified by the PICO. The publication reported that the patient did not develop new alloantibodies during their inpatient episode. Prevention of new alloantibody formation is important to clinicians, patients and their families. However, this study does not demonstrate definitively that new alloantibody formation is prevented by the intervention. Limited conclusions can be drawn from a small case study and since the study does not include a comparator, it is not possible to compare the outcomes for these patients with those receiving alternative treatments.
4.	Stabilisation of haemoglobin/cessation of haemolysis	Stabilisation of haemoglobin/cessation of haemolysis in the context of the publications is the return of Hb levels to pre-DHTR levels following a DHTR/HH episode. The publication with the strongest evidence was Chonat et al (2018) where the patient was treated with both drugs of interest identified in the PICO although order of administration of corticosteroids, IVIG, rituximab and eculizumab was not as specified by the PICO. The patient Hb stabilised at above 5g/dL by day twenty after the initial DHTR reaction. They treated with steroids as first line treatment from day one of presentation, IVIG and rituximab from day twelve and eculizumab was initiated on day fourteen alongside a blood transfusion at which point the patient's Hb levels began to stabilise. Attributing impact for

		rituximab or eculizumab alone is not possible from the information presented. Stabilisation of haemoglobin/cessation of haemolysis is important to clinicians, patients and their families. However, this study does not demonstrate that stabilisation of haemoglobin/cessation of haemolysis is reached by the intervention as there are high levels of uncertainty when drawing wider conclusions from a case study. Since the study does not include a comparator it is not possible to compare the outcomes for these patients with those receiving alternative treatments.

Considerations from review by Rare Disease Advisory Group
Not Applicable

Pharmaceutical considerations
The clinical commissioning policy proposition recommends rituximab and eculizumab for the prevention and management of delayed haemolytic transfusion reactions and hyperhaemolysis in patients with haemoglobinopathies. Neither of these medicines are licensed for this indication. Both are excluded from tariff.

Considerations from review by National Programme of Care
1) The proposal received the full support of the Blood and Infection Programme of Care on the 6th May 2020