

Soliris (eculizumab) aHUS – Exceptional Access Program Criteria

Preamble:

A confirmed diagnosis of atypical hemolytic uremic syndrome (aHUS) is required for eculizumab funding. The information below is to provide clinicians with context for how a diagnosis of aHUS will be assessed for funding consideration. Details to address these issues should be provided in the funding request.

While some patients may already have a confirmed aHUS diagnosis, by clinical history and/or genetic testing, the majority of patients presenting with thrombotic microangiopathy (TMA) have no prior diagnosis of aHUS. For most patients presenting with a TMA, it is not possible to confidently separate aHUS from the vast majority of other conditions causing TMA until after appropriate testing and treatment have occurred. The majority of patients who have TMA suffer from Thrombotic Thrombocytopenic Purpura (TTP) (30-40%), or a secondary form of TMA (e.g., pregnancy, HIV, collagen vascular disease, drugs, malignancy, stem cell transplant, malignant hypertension) (>50%), or hemolytic uremic syndrome due to a Shiga toxin (>5%) (1,2,3,4). In most cases, patients who suffer from TTP will have an ADAMTS-13 of less than 10%. If TTP has been ruled out and any secondary causes have been treated and the patient still has a persisting unexplained TMA with ADAMTS-13 $\geq 10\%$, the patient would be presumed to suffer from aHUS. Patients who present with ADAMTS-13 of $\geq 10\%$ and who are unresponsive to plasma therapy (>4 plasma exchanges) and do not have a known secondary explanation would also be presumed to suffer from aHUS.

In the absence of a confirmed diagnosis of aHUS, there is nothing in these criteria that changes the clinical expectation for appropriate use of plasma exchange/plasma infusion in the management of patients presenting with TMA.

Initiation Criteria

A patient must meet all three of the following criteria to obtain funding for initial treatment with eculizumab:

1. Confirmed diagnosis* of atypical hemolytic uremic syndrome (aHUS) at initial presentation, defined by:
 - a. Presence of an unexplained non- disseminated intravascular coagulation thrombotic microangiopathy (TMA);
- AND
- b. Baseline ADAMTS-13 activity $\geq 10\%$ on blood samples taken prior to plasma exchange or plasma infusion (PE/PI);

Note:

If the sample for ADAMTS-13 was not collected prior to PE or PI, platelet counts $> 30 \times 10^9/L$ and eGFR $< 50 \text{ mL/min/1.73m}^2$ at TMA presentation will be accepted as predictive of ADAMTS-13 $\geq 10\%$ in TMA patients. In this case, measurement of ADAMTS-13 can be taken 1-2 weeks following the last PE. The ADAMTS-13 result must be provided within 30 days of commencement of eculizumab and at least 1 week after the last PE. A one-month interim funding for eculizumab will be provided.

AND

- c. STEC-negative test in patients with a history of bloody diarrhea in the preceding two weeks.

AND

- d. Other diagnoses and causes of TMA must be ruled out, as per preamble.

2. Evidence of ongoing active and progressing TMA as defined by:

- a. Thrombocytopenia (platelet count $<150 \times 10^9/L$) that is not explained by some other cause including secondary TMA; AND hemolysis as indicated by the documentation of two of the following: red blood cell (RBC) fragmentation (schistocytes) on the blood film; low or absent haptoglobin; or lactate dehydrogenase (LDH) above normal;

OR

- b. Tissue biopsy confirming TMA in patients who do not have evidence of platelet consumption and hemolysis.

Note:

Review by external clinical expert may be required to assess requests for patients with ongoing TMA that may not clearly meet the above criteria

3. Evidence of at least one of the following documented clinical features of active organ damage or impairment:

- a. Kidney impairment as demonstrated by one of the following:
 - o A decline in estimated glomerular filtration rate (eGFR) or a rise in serum creatinine (SrCr) of $>20\%$ in a patient with pre-existing renal impairment; or
 - o SrCr $>$ upper limit of normal (ULN) for age or eGFR $< 60\text{mL/min}$ in patients who have no history of pre-existing renal impairment (i.e., who have no baseline eGFR measurement); or
 - o SrCr $>$ the age-appropriate ULN in pediatric patients (subject to advice from a pediatric nephrologist); or
 - o Renal biopsy;

OR

- b. Onset of neurological impairment related to TMA (e.g., visual field defect, hemiparesis, sensory loss, asymmetric limb weakness, confusion, loss of consciousness/coma, new onset seizure).

Note:

Patients who have extra-renal complications related to TMA (e.g., TMA-related cardiac impairment, TMA-related gastrointestinal impairment, or TMA-related pulmonary impairment) will be reviewed by an external clinical expert.

Approval duration: 6 months

Continuation Criteria (at 6 months)

After six months of eculizumab therapy, a further six month of funding will be considered if the patient demonstrates treatment response, defined as:

- Hematological normalization (platelet count, LDH, haptoglobin); AND
- An improvement or stabilization of eGFR (or SrCr); AND
- Stabilization of neurological or extra-renal impairment if these complications were originally present.

Continued treatment with eculizumab will not be funded beyond six months if a patient has experienced treatment failure, defined as:

- Dialysis-dependent at six months, and failed to demonstrate resolution or stabilization of neurological or extra-renal complications if these were originally present; OR
- On dialysis for \geq four of the previous six months while receiving eculizumab and failed to demonstrate resolution or stabilization of neurological or extra-renal complications if these were originally present; OR
- Worsening of kidney function with a reduction in eGFR or increase in SrCr \geq 25% from baseline.

Approval duration: 6 months

Continuation Criteria (at 12 months):

1. Ongoing treatment response as defined in the 6-month continuation criteria; AND
2. The patient has limited organ reserve defined as:
 - Significant cardiomyopathy, neurological, gastrointestinal or pulmonary impairment related to TMA; or
 - Grade 4 or 5 chronic kidney disease (eGFR $<$ 30mL/min). (Note: Patients who are dialysis- dependent with no significant extra-renal manifestations persisting are not considered).

There may be other exceptional circumstances where the patient has a high risk of recurrence and in whom consequences of a relapse are significant (e.g., complement Factor H genetic mutation, multiple clinical presentations of active TMA). These will be reviewed on a case-by-case basis by an external clinical expert.

For patients in whom a pause in therapy is recommended, funding will be left in place for 3 months so that eculizumab can be quickly restarted upon evidence of recurrence per recommencement criteria.

Approval duration: 12 months

Recommencement Criteria:

A patient previously diagnosed with aHUS and who responded to treatment with eculizumab and has not failed eculizumab is eligible to restart eculizumab if the following clinical conditions are met:

- Significant hemolysis as evidenced by presence of schistocytes on the blood film, or low or absent haptoglobin, or LDH above normal;

AND EITHER

- Platelet consumption as measured by either $\geq 25\%$ decline from patient baseline or thrombocytopenia (platelet count $<150,000 \times 10^9/L$);

OR

- TMA-related organ impairment (e.g., unexplained rise in serum creatinine with onset of urine dipstick positive for hemoglobin) including on recent biopsy.

Note:

1. Raised LDH alone is not a sufficient reason to recommence eculizumab, but thrombocytopenia with one marker of hemolysis (such as raised LDH, presence of schistocytes, or low/absence of haptoglobin) is an accepted reason to recommence.
2. Kidney transplantation/dialysis is not a contraindication to recommencement.

A patient who becomes eligible to restart eculizumab, in accordance with the above criteria, will be assessed every 6 months for treatment response or failure.

Approval duration: 6 months

Patients undergoing kidney transplantation:

For patients with a confirmed aHUS diagnosis who are undergoing kidney transplantation, eculizumab funding will be provided for the time period immediately prior to (or at time of) transplant and for a maximum of six months after. Treatment must be started immediately prior to or at time of transplant.

Approval duration: 6 months

All funding requests must come from, or be submitted in consultation with, a pediatric nephrologist, a nephrologist, a pediatric hematologist or a hematologist.

REFERENCES

- 1) Fujimura Y, Matsumoto M: Registry of 919 Patients with Thrombotic Microangiopathies across Japan: Database of Nara Medical University during 1998-2008. *Inter Med* 49:7-15, 2010.
- 2) George JN, Charania RS: Evaluation of Patients with Microangiopathic Hemolytic Anemia and Thrombocytopenia. *Semin Thromb Hemost* 39:153-160, 2013
- 3) Forzley BR, Sontrop JM, Mcnab JJ, Chen S, Clark WF: Treating TTP/HUS with plasma exchange: a single centre's 25-year experience. *Brit J Hematol* 143:100-105,2008.
- 4) Dahlan R, Sontrop JM, Li L, Ghadieh O, Clark WF: Primary and Secondary Thrombotic Microangiopathy Referred to a Single Plasma Exchange Center for Suspected Thrombotic Thrombocytopenic Purpura. *Amer J Nephrol* 41(6):429-437, 2015

- 5) Ardissio G, Testa S, Possenti I et al. Discontinuation of eculizumab maintenance treatment for atypical hemolytic uremic syndrome: a report of 10 cases. *Am J Kid Dis*:64(4):633-37, 2014
- 6) Ardissio G, Posenti I, Tel F et al : Discontinuation of eculizumab treatment in atypical hemolytic uremic syndrome: an update.*Am J Kid Dis*. 66(1):172-173, 2015