

# How I treat thrombotic thrombocytopenic purpura and atypical haemolytic uraemic syndrome

Marie Scully<sup>1</sup> and Tim Goodship<sup>2</sup>

<sup>1</sup>Department of Haematology, University College London Hospital, London, and <sup>2</sup>Department of Renal Medicine, Institute of Genetic Medicine, Newcastle University, Newcastle upon Tyne, UK

## Summary

Thrombotic thrombocytopenic purpura (TTP) and atypical haemolytic uraemic syndrome (aHUS) are acute, rare life-threatening thrombotic microangiopathies that require rapid diagnosis and treatment. They are defined by microangiopathic haemolytic anaemia and thrombocytopenia, with renal involvement primarily in aHUS and neurological and cardiovascular sequelae in TTP. Prompt treatment for most cases of both conditions is with plasma exchange initially and monoclonal therapy (rituximab in TTP and eculizumab in aHUS) as the mainstay of therapy. Here we discuss the diagnosis and therapy for both disorders.

**Keywords:** thrombotic thrombocytopenic purpura, atypical haemolytic uraemic syndrome, treatment, diagnosis, complement.

The last 10 years has been associated with a paradigm shift in our understanding, diagnosis, treatment and continuing clinical and basic research into Thrombotic thrombocytopenic purpura (TTP) and atypical haemolytic uraemic syndrome (aHUS) and other thrombotic microangiopathies (TMAs). Here we will concentrate specifically on TTP and aHUS, which, for many years were considered to be the same disease, but it is now clear that their pathophysiology and therapies are quite distinct. TTP results from a deficiency of ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13), a serine metalloprotease required for the cleavage of von Willebrand factor (VWF). In the majority of cases, the low ADAMTS13 levels are due to Anti-ADAMTS13 autoantibodies and an underlying disturbance in immune function. aHUS is the consequence of dysregulation of the complement system associated with gain- or loss-of-function mutations causing excessive complement activation.

However, in both disorders, further environmental and possible genetic triggers will be needed for disease presentation.

## Diagnosis of TTP and aHUS

The underlying pathophysiology of TTP is the presence of widespread microthrombi that are platelet- and VWF-rich. aHUS is associated with platelet fibrin thrombi, but other TMAs have varying amounts of lymphocytic or neutrophil infiltration as part of, or related to, the microthrombi (Hosler *et al*, 2003).

Previously, TTP was diagnosed as a pentad (thrombocytopenia, microangiopathic haemolytic anaemia (MAHA), neurological features, fever and renal involvement) and HUS was classified by the presence or absence of bloody diarrhoea. Indeed, the relevance of 'diarrhoea negative' HUS was unclear. This has now changed, and central to the diagnosis of TMAs is thrombocytopenia, MAHA and the clinical or histological effects of microvascular thrombosis. The degree of thrombocytopenia at initial presentation of TTP and aHUS is, broadly,  $<50 \times 10^9/l$  for TTP and usually  $>50 \times 10^9/l$  for aHUS. However, this is only a general rule and TTP cases with platelet counts  $>50 \times 10^9/l$  and aHUS cases with platelet counts  $<50 \times 10^9/l$  can be recalled and are not anecdotal. Therefore, a clinical suspicion and full diagnostic work up is required. Presentation may not be 'classic'. In patients presenting with neurological, cardiac or bleeding symptoms (such as haematuria) as an emergency, and is associated with thrombocytopenia, TTP should be considered. The presence of neurological and cardiovascular involvement signifies severe disease and should be considered, especially in young patients. At least 10% of presenting TTP patients require intubation and ventilation. Identification of subgroups of TTP, such as human immunodeficiency virus (HIV)-associated, pregnancy and drug-related cases, require associated treatment of the underlying condition as well as plasma exchange (PEX).

Atypical haemolytic uraemic syndrome (aHUS) is a renal thrombotic microangiopathy characterized by excessive complement activation on the surface of the renal microvasculature. It can be both sporadic and familial. Approximately

Correspondence: Dr Marie Scully, Department of Haematology, UCLH, 60 Whitfield Street, London W1T 4EU, UK.  
E-mail: m.scully@ucl.ac.uk

60% of individuals affected by aHUS also have an inherited and/or acquired abnormality affecting components of the complement pathway. These include mutations of genes encoding both complement regulators (factor H, factor I, CD46 and thrombomodulin) and complement activators (C3 and factor B) (Kavanagh & Goodship, 2011). In the United Kingdom, criteria for the diagnosis of aHUS have been established by the aHUS Rare Disease Group (RDG) (<http://rare-renal.org>). The criteria agreed for the diagnosis of aHUS are shown in Table I. When a patient presents with clinical features compatible with a diagnosis of aHUS, all other causes of a renal thrombotic microangiopathy are excluded with the investigations listed in Table II. Blood samples to be sent for measurement of complement levels (C3, C4, factor H and factor I), mutation screening (*CFH*, *CFI*, *CD46*, *C3*, *CFB*, *THBD* and *DGKE*) and detection of factor H autoantibodies should be undertaken.

Presentation of thrombocytopenia, MAHA and acute anuric/oliguric renal failure requiring dialysis, with no obvious underlying precipitant, would be in keeping with aHUS and requires urgent PEX. The caveat to this is late onset congenital TTP, which has previously been undiagnosed, but may present with renal failure as a result of recurrent, probably sub-acute TTP episodes. Therefore, an ADAMTS13 activity measurement is required, and a sample taken pre-PEX for exclusion (Fig 1).

The presence of diarrhoea may not always help differentiate these conditions and further investigations to exclude verotoxin, include stool culture, serology and/or polymerase chain reaction.

The importance of diagnosis and prompt treatment, specifically with PEX in the first instance, is to help preserve

**Table I.** aHUS diagnostic criteria.

Exclusion
Shiga toxin-associated HUS
Secondary causes
Drugs
Infection (HIV, <i>Streptococcus pneumoniae</i> )
Transplantation (bone marrow, liver, lung, cardiac but not de novo renal)
Cobalamin deficiency
Systemic lupus erythematosus
Antiphospholipid syndrome
Syndrome
Scleroderma
ADAMTS13 antibodies or deficiency
Inclusion
Renal biopsy showing a TMA
And/or
The classic triad of microangiopathic haemolytic anaemia, thrombocytopenia, renal failure

(a)HUS, (atypical) haemolytic uraemic syndrome; HIV, human immunodeficiency virus; ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; TMA, thrombotic microangiopathy.

**Table II.** Investigations to exclude other causes of a renal thrombotic microangiopathy.

TTP	ADAMTS13 activity
STEC HUS	Stool culture <i>E. coli</i> endotoxin antibodies (IgM)
APL Antibody syndrome	APL antibody
SLE	DsDNA
HIV	HIV test
Scleroderma	ANA Anticentromere antibodies Anti-ACL-70
Cobalamin C disease	Plasma homocysteine levels Plasma and urine methylmalonic acid levels

TTP, thrombotic thrombocytopenic purpura; ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; STEC-HUS, Shiga-like toxin-producing *E. coli* haemolytic uraemic syndrome; APL, Antiphospholipid; SLE, Systemic lupus erythematosus; HIV, human immunodeficiency virus; ANA, anti-nuclear antibodies; ACL, anti-cardiolipin antibody.

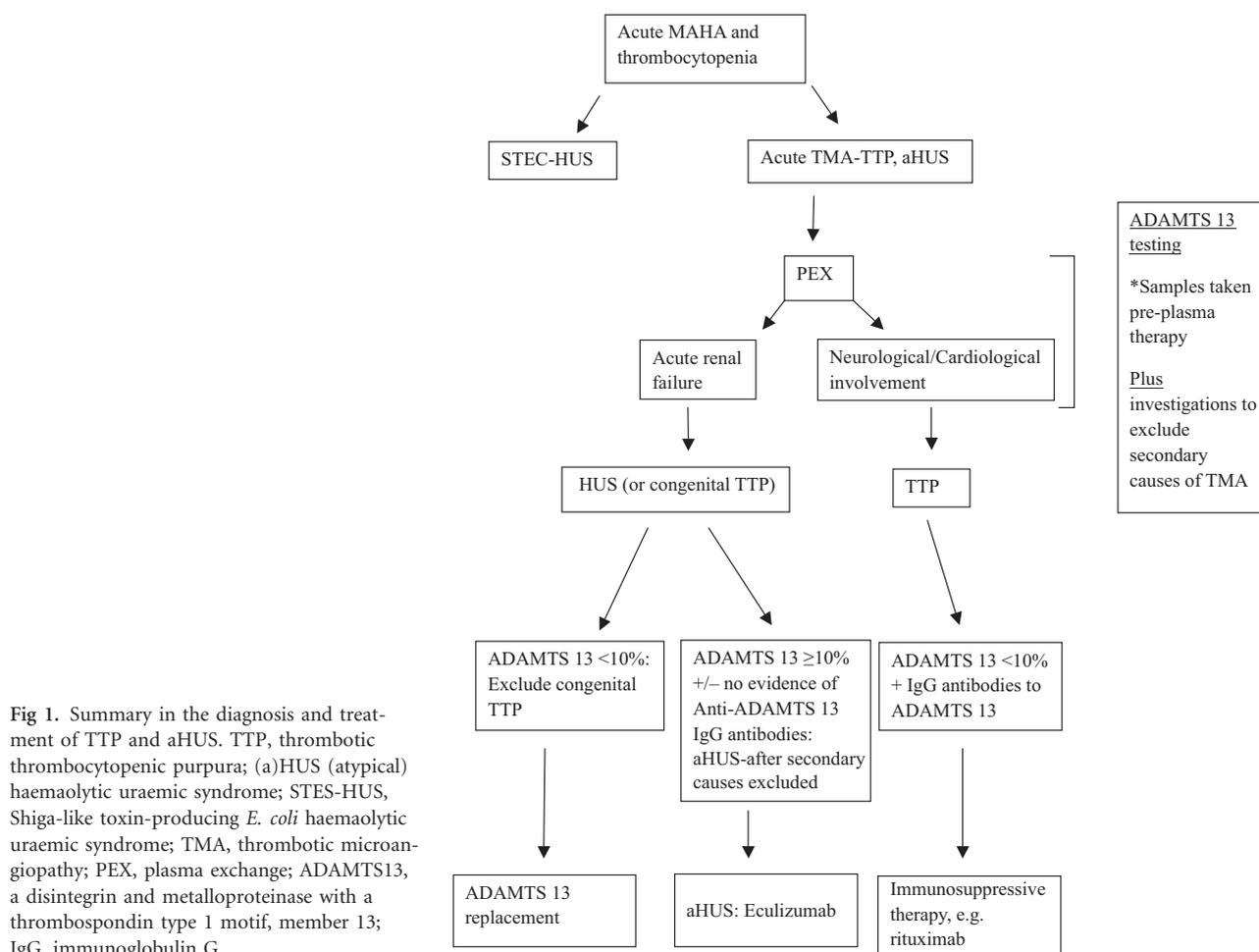
renal function in aHUS and in TTP and increase platelet counts by delivering high volumes of ADAMTS13 present in plasma, preventing organ sequelae.

Mortality in acute TTP remains at 10–20% and is up to 25% for aHUS, dependent on the mutational trigger. Therefore, on consideration of these conditions, swift referral and therapy must be instituted.

### The role of ADAMTS13 measurement in TMAs

There remains considerable debate on the role of ADAMTS13 measurements in TTP. These are fuelled by the lack of reproducibility between the various assays using VWF multimers or collagen binding, which provide an indirect measure of ADAMTS13 (Studt *et al*, 2003). They could identify very low ADAMTS13 levels but their reproducibility was poor, with very high intra-assay coefficients. More recently, fluorescence resonance energy transfer (FRETs) assay has become the main methodology of choice for many institutions undertaking ADAMTS13 assays, but other assay methods are used, such as mass spectrometry and enzyme-linked immunosorbent assay, e.g., technozyme (Technoclone, Vienna, Austria) (Tripodi *et al*, 2004; Peyvandi *et al*, 2010).

Atypical HUS, and other TMAs by definition, will not have low (<10%) ADAMTS13 activity or the presence of significant Anti-ADAMTS13 immunoglobulin G (IgG) autoantibodies. In contrast, idiopathic TTP will have low ADAMTS13 activity (<10%) and, in the majority of cases (excluding congenital TTP), antibody can be detected. It has been suggested that there are cases of normal ADAMTS13 activity in TTP, but in our experience, these have turned out to be other diagnosis such as aHUS, mainly associated with *CD46* mutations. Assuming a sample has been taken pre-PEX, a mid range/normal ADAMTS13 is not consistent with



**Fig 1.** Summary in the diagnosis and treatment of TTP and aHUS. TTP, thrombotic thrombocytopenic purpura; (a)HUS (atypical haemolytic uraemic syndrome; STEC-HUS, Shiga-like toxin-producing *E. coli* haemolytic uraemic syndrome; TMA, thrombotic microangiopathy; PEX, plasma exchange; ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; IgG, immunoglobulin G.

TTP. The only subgroup of TTP with ADAMTS13 activity that is not low (<10%) is pancreatitis-associated TTP (McDonald *et al*, 2009).

Atypical haemolytic uraemic syndrome may have a normal ADAMTS13 at presentation or it can be reduced, usually to about 30–40%. Similar results can be seen in other TMAs, such as malignant hypertension, scleroderma, autoimmune-mediated TMA and transplant-associated TMA. The reason some secondary cases have a normal ADAMTS13 at presentation and some are reduced is unclear. It may be because of the raised VWF/thrombin levels, which result in consumption of ADAMTS13, but this does not explain the full picture.

### Differentiating TTP from aHUS

It has been suggested that unless there is prompt availability of ADAMTS13 assays, a serum Creatinine level >150–200  $\mu\text{mol/l}$  or a platelet count >30  $\times 10^9/\text{l}$  almost always eliminates a diagnosis of severe ADAMTS13 deficiency (Zuber *et al*, 2012a). While the overall Creatinine levels in TTP cases are not increased and platelet counts are more

usually reduced, i.e., <30  $\times 10^9/\text{l}$ , in large cohorts, there is enough evidence in daily practice of patients with TTP who have renal dysfunction or a platelet count >30  $\times 10^9/\text{l}$  (Scully *et al*, 2008; McDonald *et al*, 2009; Coppo *et al*, 2010). However, we would suggest that samples are taken for ADAMTS13 testing to differentiate the disorders, before patients initiate PEX.

### Treatment

When a diagnosis of an acute TMA has been made, suggesting TTP or aHUS, it is imperative that patients are transferred to specialist centres for treatment as soon as possible.

#### How I treat TTP

Thrombotic thrombocytopenic purpura is a haematological emergency. Referral to an apheresis unit, ensuring central venous line access and defrosting of plasma, may result in delays to initiation of treatment. However, patients should not be left overnight without PEX. Therefore, provision of centres with a 24/7 apheresis service is required. If there is a

delay in transfer, pulsed methyl prednisolone and plasma infusion should be considered (Scully *et al*, 2012).

Plasma exchange is the most important treatment, as it replaces large volume of plasma containing the missing enzyme and in removes the associated anti-ADAMTS13 IgG antibody, which is directly related to the pathogenesis of the disease. In conjunction, high dose steroids, either oral prednisolone or pulsed methylprednisolone, should be used. While determining the underlying precipitant, steroids should be considered.

Severe initial disease or progression of symptoms during admission may require that PEX is intensified, for example to twice daily, or increased from 1.0 to 1.5 plasma volumes. With an improvement in counts and clinical condition, PEX can be continued as a daily, single plasma volume. There is no indication to taper PEX, assuming close surveillance once PEX is stopped.

Further treatment modalities to improve response should then be instituted. For example, highly active anti-retroviral therapy (HAART) should be commenced in patients for whom a diagnosis of HIV-TTP is made. Therapy should be given after PEX and triple or quadruple therapy is preferable initially (Hart *et al*, 2011). As the majority of cases are idiopathic TTP, with no precipitating cause and antibody-mediated, further immunosuppressive therapy should be considered. Ciclosporin is used, with satisfactory results. However, it is poorly tolerated by patients and currently rituximab is preferable.

#### *Adjuvant therapy in the treatment of TTP*

There is a widespread national and international experience with rituximab in idiopathic TTP. However, there remain a number of questions regarding the timing, dose and frequency of therapy and it has not been used in a randomized control trial setting.

Initial data showed, and confirmed in individual cases, small series and larger cohorts (relative to the disease incidence), the benefit of rituximab in relapsing and refractory TTP (Chemnitz *et al*, 2002; Gutterman *et al*, 2002; Zheng *et al*, 2003; Ahmad *et al*, 2004; Sallah *et al*, 2004; Fakhouri *et al*, 2005; Reddy *et al*, 2005; Scully *et al*, 2007; Jasti *et al*, 2008; Ling *et al*, 2009; de la Rubia *et al*, 2010). Indeed, funding restrictions are such that, in some areas, this remains the point at which rituximab is used. A phase II non-randomized trial to demonstrate the efficacy and safety of rituximab compared to historical controls, showed the benefit of Rituximab administration in acute TTP. In Caucasian patients, there was a reduction in the number of PEX required to achieve remission and an overall (excluding cases treated in the Intensive Care Unit) reduction in inpatient days, which was also seen in the group overall compared to historical controls (Scully *et al*, 2011).

The standard rituximab dose of 375 mg/m<sup>2</sup> has been used almost extensively in the literature to achieve B cell-depletion in TTP. There is little evidence of low dose rituximab

regimes in acute disease. Furthermore, despite B cell depletion measured by CD19 levels, they do not always correlate with ADAMTS13 autoantibody reduction acutely and remission and are not helpful in predicting relapse.

As per the lymphoma protocol, based on convenience with other chemotherapy infusions in this disease, rituximab was used weekly. However, confirmation of clearance of the anti-CD20 therapy in PEX fluid and a review of peak and trough rituximab levels with PEX has resulted in a move to infusing rituximab every 3–4 d (McDonald *et al*, 2010).

Regardless of the timing of starting Rituximab in an acute TTP episode, the responses take a median of 10 d. Therefore, starting Rituximab earlier in an acute episode will result in reduced PEX, quicker over all responses and reduced inpatient admissions, with significant clinical and financial benefits (Westwood *et al*, 2013).

From the phase II trial, an unexpected finding was the reduction in relapse rates with acute TTP. Before rituximab, immunosuppressive therapies had not generally shown a consistent sustained benefit. This appears, from our historical control cases, to be as a result of failure to increase the ADAMTS13 activity by reducing antibody levels. In patients who do relapse after rituximab, the median time is 24 months, but far longer periods of remission are seen. This is in contrast to many having had multiple repeated episodes in the pre-rituximab era and immunosuppressive therapy that had unacceptable side effects. The low relapse rate was considerable and confirmed in a further multicentre trial in relapsed/refractory acute TTP cases presented by the French collaborative group (Froissart *et al*, 2012). Previously documented relapse rates are between 30% and 50%. The Oklahoma registry had a 34% relapse rate in 60 TTP cases between 1989 and 2008, with ADAMTS13 activity <10% at diagnosis (Kremer Hovinga *et al*, 2010).

#### *Monitoring patients following an episode of acute TTP*

In the majority of acute idiopathic TTP cases, treatment is associated with a reduction in anti-ADAMTS13 IgG levels and an increase in ADAMTS13 activity. The risk of relapse of TTP is associated with low ADAMTS activity and or the presence of antibody. Our practice is to monitor patients in clinical remission with normal ADAMTS13 activity. A reduction in enzyme (<10%) is a marker to consider elective treatment with rituximab, which results in normalization of ADAMTS13 activity and prevents an acute episode (Westwood *et al*, 2013).

The reduction in ADAMTS13 activity may occur some months before relapse, especially in Afro-Caribbean patients, whereas in Caucasians, relapse typically occurs sooner if left untreated. ADAMTS13 is a useful surrogate marker of potential relapse, but the timing of relapse is variable and the use of prophylactic rituximab may be guided by the patient's previous history. Monitoring does not provide an absolute guarantee against relapse and patients need to be vigilant.

Within the elective therapy setting, we have used low dose rituximab (100 mg/m<sup>2</sup>), for which an increase in ADAMTS13 activity can be documented and relapse possibly prevented.

#### *Failure to achieve normalization of ADAMTS13 activity despite remission*

There are a small percentage (approximately 5%) of patients who may attain clinical remission, although this is typically associated with a longer acute admission, but the ADAMTS13 activity does not improve and remains low (<10%). These patients are very difficult to monitor regarding relapse and need to seek urgent medical attention for a blood count if unwell. However, a useful combination has been rituximab and mycophenolate, which has achieved normalization of levels in patients who previously have not demonstrated a rise in ADAMTS13 activity. However, these cases do still need regular monitoring and if ADAMTS13 activity falls (<10%), further rituximab therapy is given. Once again, although not exclusively, these are typically Afro-Caribbean patients and a further understanding of the pathophysiology of these cases is required, together with the development of other therapies.

Other immunosuppressive treatments have been documented in the literature. Ciclosporin is effective (Cataland *et al*, 2007a,b), but we have not used it since the advent of monoclonal therapy for a number of reasons, including the risk of relapse during/on stopping treatment. Furthermore, patients do not tolerate side effects, particularly young females.

#### *Congenital TTP (also known as Upshaw-Schulman syndrome)*

Despite being a rare subtype, this is increasingly being diagnosed, both in young children and late onset associated with pregnancy. Patients require monitoring of their platelet counts and therapy to ensure platelets remain  $>150 \times 10^9/l$ . The frequency of treatment will vary with the age of presentation and the patient's genotype. Failure to achieve normal platelet counts will result in end organ damage, including renal failure, neurological or cardiac features. Normalization can be achieved with either plasma infusions (non-UK sourced and virally inactivated-Octaplas<sup>®</sup>; Octapharma, Vienna, Austria) or with an intermediated purity Factor VIII concentrate, which contains measurable ADAMTS13 (Bio-Products Laboratory, Elstree, Herts, UK).

In women of child-bearing age, pregnancy requires regular plasma infusion throughout to ensure improved outcomes for mother and baby.

#### *Pregnancy-associated TTP*

Pregnancy may be a precipitant of TTP in a small proportion of cases and ADAMTS13 analysis is required to differentiate

congenital from acquired TTP. TMAs in pregnancy can be difficult to differentiate, e.g., pre-eclampsia (PET), HELLP syndrome (haemolysis, elevated liver enzyme levels, and low platelet counts) and TTP. In general, HUS occurs in the postpartum period. TTP may be associated with features suggestive of PET or HELLP. As a general guide, PEX should be started in patients with platelet counts  $<50 \times 10^9/l$  and MAHA features or the presence of clinical features possibly suggestive of TTP at higher platelet counts.

#### *How do I treat incident patients with aHUS?*

Until recently it was recommended that all patients presenting with aHUS should be offered a trial of PEX and/or plasma infusions (Taylor *et al*, 2010). Despite this, the majority of patients need long term renal replacement therapy within 2 years of presentation (Noris *et al*, 2010). With the finding that excessive activation of the alternative pathway of complement underlies the pathogenesis of aHUS in most patients, it became clear that complement inhibition would be a logical therapy. Eculizumab is the only complement inhibitor currently licensed for any indication. It was first introduced for the treatment of paroxysmal nocturnal haemoglobinuria (Hillmen *et al*, 2006) and long term data has shown its efficacy in this disease (Kelly *et al*, 2011). Anecdotal reports of its efficacy in aHUS (Gruppo & Rother, 2009; Nurnberger *et al*, 2009) led to clinical trials, the results of which have recently been published (Legendre *et al*, 2013). These showed that eculizumab was a highly effective treatment for aHUS in patients who were either resistant to PEX or dependent on regular PEX to maintain remission. Based on these results, in 2011 both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) approved the use of eculizumab for the treatment of aHUS. In England an application was submitted to the Advisory Group for National Specialised Services (AGNSS) for a national service for aHUS, including funding for eculizumab. This was considered by AGNSS in June 2012. In January 2013 it was announced that 'they concluded that eculizumab would help save lives and improve the quality of life for children (among whom the condition is particularly prevalent) and adults with atypical haemolytic uraemic syndrome.' (<http://www.specialisedservices.nhs.uk/document/eculizumab-treatment-atypical-haemolytic-uraemic-syndrome/>). Subsequently 'Ministers agreed with AGNSS that there is evidence for the clinical effectiveness of eculizumab for the treatment of atypical haemolytic uraemic syndrome but wanted further advice on the affordability of the drug'. Ministers have asked NICE to consider eculizumab for the treatment of atypical haemolytic uraemic syndrome as part of its new Highly Specialised Technologies programme.' The outcome of the National Institute for Health and Care Excellence (NICE) evaluation will be announced in 2014. In the meantime, National Health Service (NHS) England has published a Clinical Commissioning Policy Statement on the use

of eculizumab for aHUS (<http://www.england.nhs.uk/wp-content/uploads/2013/09/e03-hss-a.pdf>). This states that NHS England will commission eculizumab for new patients with aHUS and for patients who are on dialysis and are suitable for a kidney transplant. In England, we are therefore now able to treat all new patients with aHUS. This service is delivered locally but coordinated through the expert centre in Newcastle. When a patient presents with features compatible with a diagnosis of aHUS we request that the investigations listed in Table II are undertaken. We try to initiate treatment with eculizumab as soon as possible because the clinical trials have suggested that the sooner that treatment is started, the greater is the chance of recovery of renal function. The only result that we request be available is the ADAMTS13 activity. If the ADAMTS13 activity is not immediately available we recommend that treatment with PEX is commenced and continued until the result is available. Provided that the ADAMTS13 activity is not <10% and that the clinical features are compatible with a diagnosis of aHUS we, with the approval of NHS England, authorize the onset of treatment with eculizumab. If subsequent investigations show that the thrombotic microangiopathy is due to another condition apart from aHUS, then eculizumab is withdrawn. The results of the genetic investigations are available within 8 weeks.

Two groups have recently published reports of mutations in the *DGKE* gene, encoding diacylglycerol kinase epsilon (DKGE) in young children with the clinical phenotype of aHUS (Lemaire *et al*, 2013; Ozaltin *et al*, 2013). *DGKE* is a lipid kinase that catalyses the conversion of diacylglycerol to phosphatidic acid. Failure of this leads to increased protein kinase C activity and it has been postulated that this is responsible for the development of a TMA (Quaggin, 2013). This form of aHUS presents usually in the first year of life and does not respond to eculizumab. The mutations in *DGKE* are either homozygous or compound heterozygous. If, on screening, we find such changes in *DGKE* in the absence of any mutations in complement genes, then we will consider withdrawing eculizumab.

The markers of an active TMA (thrombocytopenia, microangiopathic haemolytic anaemia, elevated lactate dehydrogenase, low haptoglobin) respond rapidly to treatment with eculizumab in virtually all patients with an underlying complement abnormality. In aHUS, whether renal function returns is dependent on the extent of irreversible renal damage sustained before the onset of treatment. In both anecdotal reports and the trials it has been found that some patients who are on dialysis at the onset of the treatment will recover sufficient renal function to stop dialysis. This can take several months. We, therefore, currently would not consider withdrawing eculizumab in a dialysis-dependent patient until they had received at least 4 months treatment with eculizumab. If eculizumab is withdrawn in such a patient then we monitor closely the TMA markers. If there is any evidence of recurrent extra-renal TMA then eculizumab is

reinstated. The other group of patients in whom we will consider withdrawing eculizumab is those in whom we subsequently find a mutation in *CD46* in the absence of changes in any other gene. We counsel this patient that there is a risk of recurrent disease and withdrawal of the eculizumab is only undertaken if the patient agrees to this. If not then they continue on eculizumab indefinitely.

At present, in all other patients we continue treatment with eculizumab indefinitely. The major risk associated with eculizumab treatment is the development of meningococcal disease. All patients are vaccinated with a tetravalent vaccine before the onset of treatment and, in addition, receive long-term prophylactic antibiotics (either penicillin or erythromycin) because current vaccines do not cover Serogroup B strains. We will in the future be testing the response to vaccination after 12 weeks and re-vaccinating if the response is suboptimal.

#### *How do I treat prevalent aHUS patients?*

The outcome of renal transplantation alone in aHUS patients on dialysis has been well documented to be poor, with a high rate of graft loss due to recurrent disease (Bresin *et al*, 2006; Le *et al*, 2013). Because of this, many patients known to have complement abnormalities associated with a high risk of recurrence have not been listed for a transplant. In those patients known to have mutations in the genes encoding complement proteins synthesized predominantly by the liver (such as factor H and factor I), combined liver-kidney transplant is an alternative therapeutic strategy that can be successful (Saland *et al*, 2009). However, the 1-year patient survival for this procedure is not as high as would be expected with a kidney transplant alone. Because of this and the advent of eculizumab, many patients do not opt for this procedure. Both anecdotal reports and trial data have shown that eculizumab can be used successfully to both treat and prevent recurrent disease post-transplant (Zuber *et al*, 2012b). In England, aHUS patients on dialysis are now, therefore, being listed for a kidney transplant that is covered by eculizumab given immediately prior to transplantation and then long term to prevent recurrent disease. Whether in any of these patients it will be safe to withdraw eculizumab at a later stage not yet known.

There are a small number of aHUS patients who respond to PEX, but need long-term therapy to maintain their remission. Most of these patients entered the clinical trials and are now receiving long-term eculizumab. We recommend that those few who are still on PEX should be started on eculizumab and PEX withdrawn.

There are also a small number of patients who have responded to PEX and have stayed in remission without any prophylactic therapy. Screening in some of these patients has shown a pathogenic complement gene mutation. We believe that such patients are potentially at risk of recurrent disease in the future. Whether this warrants prophylactic treatment

with eculizumab is uncertain. We currently discuss this with the individual patient.

## Conclusion

The initial diagnosis and treatment of TMAs, specifically TTP and aHUS with PEX remains paramount, but is more justified as we understand different disease states. However, determining the underlying pathophysiology and diagnosis is relevant when further therapeutic modalities need to be introduced into the treatment pathway. The advent of

eculizumab has dramatically changed the prognosis of aHUS. It is now possible that early treatment will prevent irreversible renal failure in patients who present for the first time and that recurrent disease can be prevented in those patients undergoing renal transplantation. Similarly, prompt diagnosis and initiation of PEX and monoclonal anti-CD20 treatment in TTP has improved response and relapse rates.

## Author contributions

MS and TG equally contributed to the writing of the paper.

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