THE MULTIPLE FACETS OF THROMBOTIC MICROANGIOPATHIES

Summary of Presentations from the Alexion-Sponsored Symposium, held at the 19th EHA Congress, Milan, Italy, on 12th June 2014

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MEETING SUMMARY

The Alexion satellite symposium was introduced by Prof Pier Mannuccio Mannucci who provided an introduction to the history of thrombotic microangiopathies (TMAs). Prof Paul Coppo gave an overview of TMAs and the differential diagnosis of atypical hemolytic-uraemic syndrome (aHUS) and thrombotic thrombocytopaenic purpura (TTP). He emphasised the importance of a suitable differential diagnosis in order to initiate an appropriate treatment as soon as possible, eventually allowing better patient outcomes. Prof Javier de la Rubia discussed the role of the complement pathway and how genetic abnormalities can lead to dysregulation in aHUS. Prof Thorsten Feldkamp concluded by giving an overview of the latest clinical trial data on the efficacy and safety of eculizumab in the management of aHUS.

Differential Diagnosis of TMAs

Professor Paul Coppo

TMAs are a group of heterogeneous and rare diseases (<4 cases per million/year). Each disease is characterised by different features and pathophysiological mechanisms. It is possible to distinguish TTP from other TMAs. TTP is mostly an acquired disorder but can also be congenital. Another TMA is HUS, which is caused by Shiga-toxin producing bacteria (STEC-HUS) or complement dysregulation (aHUS). TMAs can also be observed in other contexts such as in the HELLP syndrome in pregnant women, in catastrophic antiphospholipid syndrome, malignant hypertension in cancer patients, and in transplantation. TMAs all have a specific pathophysiology, a specific management, and a specific prognosis.

The pathophysiology of TTP was first described in 1924 by Eli Moschcowitz[1] following the case of

a young girl who suddenly presented with fever, cerebral manifestations, anaemia, hemorrhage, and renal failure. She experienced heart failure and died after 2 weeks. The autopsy showed thrombi in the arterioles and capillaries of most organs. TTP typically involves the brain but its effects are not limited to the brain. Autopsy studies have shown that TTP is a multi-system disorder involving the heart, pancreas, kidney, adrenal glands, digestive tract, and liver.[2]

The pathophysiology of TTP can be explained by the action of von Willebrand factor (VWF). VWF is synthesised and separated by endothelial cells in the plasma as very large multimers (500–20,000 kDa), which are cleaved by ADAMTS13 to lower molecular weight multimers,[3] decreasing their adhesiveness to platelets. TTP patients have a severe deficiency of ADAMTS13 resulting in the accumulation of larger multimers in plasma causing platelet aggregation.[4,5] This eventually results in the formation of microthrombi in the microcirculation leading to multi-organ failure. ADAMTS13 is a metalloproteinase that belongs to the ADAMTS family. Deficiencies of ADAMTS13 can arise from heterozygous bi-allelic mutations of the gene,[6] corresponding to the rare congenital cases of TTP. More commonly, deficiencies result from auto-antibodies directed against the enzyme. These patients can be treated efficiently with plasma therapy, which allows them to receive ADAMTS13 exogenously.

HUS arises from ingestion of the Shiga-toxin via contaminated food or water. The Shiga toxin crosses the digestive barrier and is transported by leukocytes to the endothelial cells of the renal microvasculature. The toxin is internalised in the endothelial cells, leading to the expression of proaggregant and procoagulant molecules such as VWF and tissue factor, which leads to the formation of fibrin-rich microthrombi. Deposits of complement, such as C3 and C9, are also found on the surface of platelets, monocytes, and circulating endothelial microparticles. These complement fragments may therefore be involved in STEC-HUS as well.

The complement system is composed of three pathways: the classical pathway, which is activated by immune complexes; the alternative pathway, which is activated by microbial surfaces; and the lectin pathway, which is activated by sugars on the surface of microbes. In the last 20 years, dysregulation of complement has been found to be linked to the development of aHUS. Mutations in complement regulatory genes are found in approximately 70% of patients with aHUS.[7]

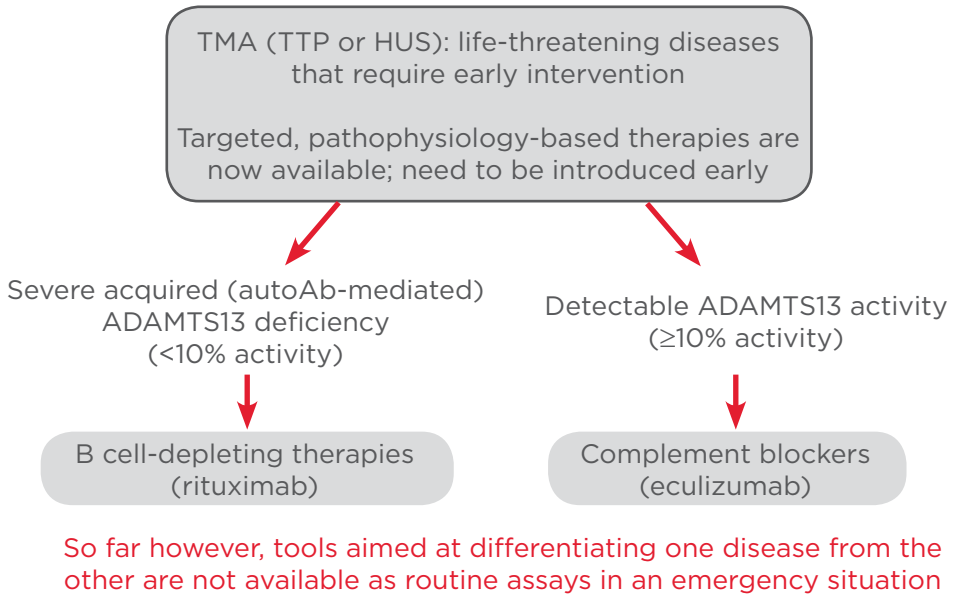

Figure 1: The dilemma of TMA management.
HUS: hemolytic-uraemic syndrome; TMA: thrombotic microangiopathy; TTP: thrombotic thrombocytopaenic purpura.
Modified from Sadler[9] and Tsai.[10]

The type of mutation impacts the prognosis of the patient, with mutations in Factor H having the poorest prognosis in terms of renal function, and patients are known to relapse even after renal transplant.[8] The mutation MCP/CD46 is the least severe in paediatric-onset patients. However, all mutations have a strong impact in terms of overall survival and renal function, highlighting the need for new therapies for these patients.

TMAs are life-threatening disorders that require early intervention. In patients with a severe ADAMTS13 deficiency (<10% activity) it is necessary to supply the missing enzyme. If there is an antibody against the enzyme, then immunosuppressive drugs, such as rituximab, are required to be administered particularly in patients who experience a suboptimal response to standard treatment. In patients with detectable ADAMTS13 activity (≥10% activity), complement blockers such as eculizumab are introduced. However, assays to differentiate one disease from another are not yet readily available (Figure 1).[9,10]

One reference method used to measure ADAMTS13 activity is by using the FRETS assay.[11-13] This assay is only available in specialised laboratories and emergency testing is limited by the need to transport the sample. However, the result is available in <1 day.[12] The FRETS assay has been used in a large number of patients from multicentre studies. Commercial kits are also available, which can provide results within a day.[14,15] However, these assays have not yet been validated between laboratories for routine use; therefore, their use for patient care requires further evaluation.

Efforts were made to set up a predictive score to help identify severe ADAMTS13 deficiency. Patients with an idiopathic form of TMA were assessed to see whether it was possible to predict a severe ADAMTS13 deficiency by assessing clinical features and standard biology. The characteristics of patients with a severe ADAMTS13 deficiency were compared with patients with detectable ADAMTS13 activity. The results showed that patients with a severe ADAMTS13 deficiency displayed a more severe thrombocytopaenia compared to patients with detectable ADAMTS13 activity at initial presentation. It was also observed that patients with detectable ADAMTS13 activity had a more severe renal involvement. In fact, 21% of these patients had end-stage renal disease (ESRD).[16,17]

These differences were used to establish a predictive score to identify patients with ADAMTS13 deficiency and ensure an appropriate therapy for treatment, and it was found that creatinine below 200 µmol/L and a platelet count <30,000/mL^3 at presentation were strongly associated with severe acquired ADAMTS13 deficiency.[16,17] Other studies have also confirmed patients with severe ADAMTS13 deficiency are more thrombocytopaenic and have lower creatinine levels at presentation than patients with detectable ADAMTS13 activity.[18-21]

Patients with a diagnosis of TMA often require urgent specific treatment, therefore it is important to identify quickly whether the disease is TTP or aHUS. Briefly, children with a clear diagnosis of aHUS are now usually treated front-line with eculizumab. Adult patients with a newly diagnosed TMA still undergo plasma exchange. An associated context that may impact prognosis and treatment such as pregnancy, transplantation, HIV infection, cancer, or chemotherapy, infection-associated STEC-HUS should be rapidly identified. A patient with an apparently idiopathic TMA responding well to the treatment will show recovery of the platelet count and creatinine level, resulting in a decreased need for plasma exchange sessions. In patients with a suboptimal response by day 5, those with a severe acquired ADAMTS13 deficiency (consistent with the diagnosis of acquired TTP) should be treated with rituximab in association with daily plasma exchange.[17] In contrast, a detectable ADAMTS13 activity suggests the diagnosis of aHUS and administration of eculizumab with plasma exchange interruption should be considered.[17]

In conclusion, individual TMAs can no longer be classified as the same disease; rather the different types of TMA can be differentiated according to their underlying pathological mechanism. Although TMAs such as TTP and HUS are life-threatening, their prognosis may be favourable provided that a rapid diagnosis is made and the appropriate treatment regimen is applied. Measurement of ADAMTS13 activity is the recommended test used to distinguish aHUS from TTP, while taking into account the clinical features of the particular TMA. The rarity of these diseases makes their diagnosis challenging; therefore, it is important for clinicians to be fully aware of the diagnostic features of the different types of TMA.

aHUS and the Role of Complement

Professor Javier de la Rubia

The complement system is part of the innate immune system and is composed of approximately 30 plasma and membrane-bound proteins. The main functions of the complement system are to fight infections, eliminate immune complexes, and destroy and remove autologous damaged cells.[22] The three pathways of the complement system (alternative, classical, and lectin) generate different enzyme complexes, C3 convertases, that cleave C3 to C3a and C3b. C3a is an anaphylatoxin and C3b targets the cells to subsequently be destroyed. The alternative pathway is always active at a low level (tick over). C3b is further amplified via a strong self-amplifying feedback loop. The C3 convertases hold a strategic position, can be exponentially and strongly activated, and control complement activation. C3b then binds to the C3 convertase to form C5 convertase, which cleaves C5 into C5a and C5b. C5b then initiates the assembly of later complement components, including C5b-9, resulting in the formation of the membrane attack complex leading to cell destruction.[23] This sequential activation is potentially dangerous for the host. Fortunately, there is a group of complement components such as complement Factor I and complement Factor H,[23] which perform a regulatory function so that in a normal situation all host tissues are protected against damage by autologous complement (Figure 2). It is precisely this equilibrium between complement activation and regulation that is disrupted in aHUS patients. All complement proteins that have been found mutated in these patients participate in the generation and further inactivation of the C3b molecule through the alternative pathway. Many patients experience prolonged apparently symptom-free periods in spite of having persistent underlying abnormalities in complement activation. These features indicate that multiple, concurrent genetic and environmental triggers are needed to determine complete disease expression. Therefore, external triggers (such as common infection, surgery, pregnancy, or autoimmune diseases) in conjunction with a genetic abnormality in the complement system may cause the onset of the disease.[24,25]

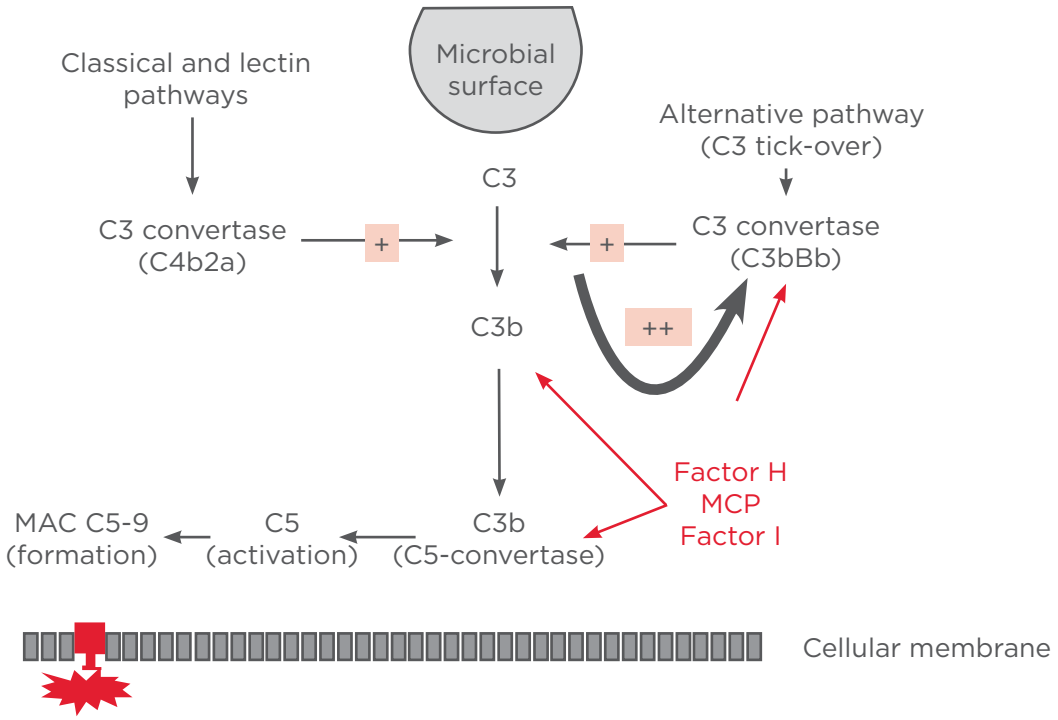

Figure 2: Role of complement in aHUS.
aHUS: atypical hemolytic-uraemic syndrome; MAC: membrane attack complex; MCP: membrane cofactor protein.
Modified from Noris et al.[23]

In aHUS patients, once an environmental trigger initiates the complement cascade beyond a critical threshold, C3b formation and deposition occur on vascular endothelium, which leads to further complement activation through the alternative pathway self-amplifying loop, activation of platelets and leukocytes culminating in microangiopathic injury and thrombosis. There is excessive activation of C3 convertase, causing consumption of C3 and production of C3a and C3b. C3b molecules are then deposited on the endothelial cell surface erroneously (self), targeting them for cell damage and destruction. aHUS is a permanent, ongoing, systemic disease that is defined by the clinical characteristics of TMA; a decrease in platelet count, microangiopathic hemolysis, and organ damage or impairment.

More than 120 different mutations, accounting for 50-60% of cases, have been discovered; the majority in the past 20 years.[26] Proteins such as complement Factor H, complement Factor I, or MCP are complement regulators, and a mutation in these will lead to uncontrolled complement activation. Mutations in C3 and Factor B, can result in the generation of a hyperactive C3 convertase that is resistant to regulation. Not all aHUS patients have an identified underlying genetic abnormality. In fact, complement mutations have been detected in approximately 50% of aHUS patients; therefore, diagnosis of aHUS does not require identification of a genetic mutation.[7,8] Although C3 is consumed in aHUS it is not a reliable marker for diagnosis of the disease as C3 is normal in most patients with aHUS. The reason is that in most cases of aHUS, C3 consumption takes place locally on the surface of the endothelium and thus, it is difficult to detect with classical C3 level measurements.[8,27]

aHUS is a disease of poor prognosis; studies have shown that 33–40% of patients die or progress to ESRD within the first clinical manifestation despite the use of plasmapheresis.[7,28] aHUS is a systemic disease, and so it is important to assess all organ dysfunction when managing patients. Hematologic improvement (platelets and hemolysis) may not necessarily reflect functional improvement of other organs.

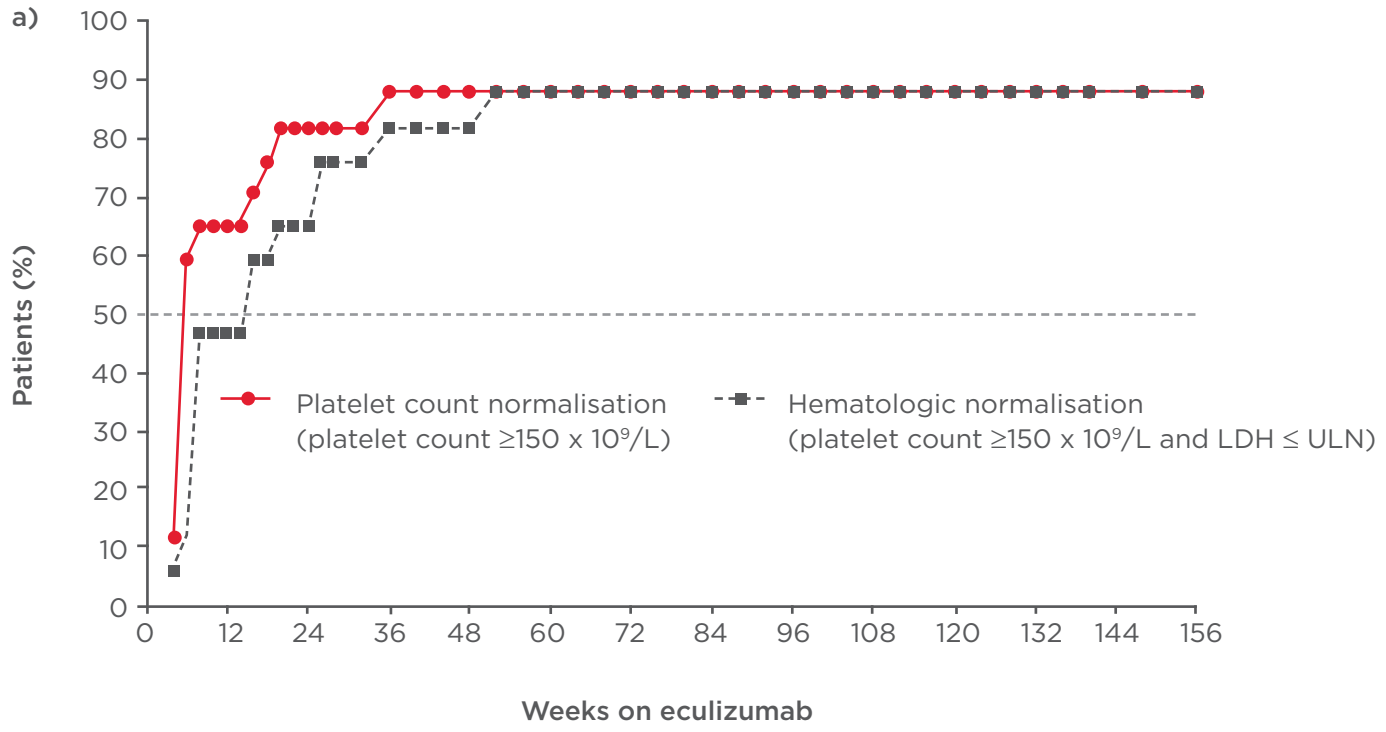

Figure 3: Time to improvement in key hematological parameters in patients with aHUS and progressing TMA (C08-002 trial; n=17).
aHUS: atypical hemolytic-uraemic syndrome; LDH: lactate dehydrogenase; TMA: thrombotic microangiopathy; ULN: upper limit of normal.
Modified from Legendre et al.[29,35]

Management of HUS in 2014

Professor Thorsten Feldkamp

Until recently, plasma exchange/plasma infusion (PE/PI) was the only option available for the management of patients with aHUS. However, many patients were progressing to ESRD despite PE/PI. Studies have shown that 56% of adult patients suffer from ESRD after 1 year, and that after 5 years 64% of patients have ESRD.[8] This is a devastating outcome and although dialysis can be used to compensate for the loss in renal function, it is not an ideal approach due to the associated practical difficulties and its association with extremely high cardiovascular risk and mortality. These factors highlight the need for another treatment option for patients with aHUS.

Eculizumab is a new drug that has been approved for the treatment of aHUS. Eculizumab works by inhibiting cleavage of C5, thus blocking activation of the terminal complement pathway.[23] The clinical development programme of eculizumab consisted of almost 100 patients in total in prospective clinical trials. The outcome of two of these trials supported the approval of eculizumab in 2011,[29] and long-term extension studies are being conducted.[30,31] An aHUS registry is also being developed.[32] This registry will not only include patients from the eculizumab clinical development programme but also all patients that have aHUS, regardless of whether they are being treated with eculizumab. It is anticipated that this registry will, on one hand, broaden our knowledge of eculizumab treatment but also, on the other hand, enhance our understanding of the symptoms and clinical course of aHUS in general.

In terms of the clinical trial patient populations, the first of the three trials (the so-called 'chronic' or C08-003 trial) included patients with a long duration of aHUS and chronic kidney disease (CKD).[29] These patients were undergoing chronic PE/PI and were required to have stable platelets but also had evidence of renal damage and ongoing hemolysis. These patients were switched from PE/PI to eculizumab. The second trial (the so-called 'resistant' or C08-002 trial) enrolled patients with aHUS and progressing TMA.[29] These patients had severe TMA; indicated by evidence of hemolysis, renal damage, and rapid drop in platelets. As a requirement for the study inclusion patients then had to undergo at least four sessions of PE/PI. If these sessions were ineffective, showing that the disease process was plasma resistant, the patients could be included in the trial. In the last study, the C10-004 trial, patients had to meet specific inclusion criteria with regards to platelet count, hemoglobin, LDH, and serum creatinine in order to be enrolled, but there was no specification in terms of need for PE/PI.[33] In all trials, patients were required to have ADAMTS13 activity >5% (to rule out TTP) and no evidence of Shiga-toxin-induced HUS. Identification of genetic mutations in the complement pathway was not a requirement for enrolment.

The key endpoints for the studies were improvement in platelet count from baseline, TMA event-free status (composite endpoint: no decrease in platelet count >25% from baseline, no new dialysis, and no new plasma exchange or plasma infusion for 12 consecutive weeks), hematological normalisation (normal platelet counts and lactate dehydrogenase [LDH] at two consecutive measurements, 4 weeks apart) and TMA intervention rate (number of events [plasma exchange or infusion, dialysis, or both]/patient/day).[29] In patients with aHUS and progressing TMA (C08-002 trial) at 2 years of sustained eculizumab treatment, platelet normalisation was achieved in 87% of patients (Figure 3), TMA event-free status was achieved in 88% of patients, and 88% achieved hematological normalisation. In addition, there was a reduction in TMA intervention rate from 0.88 to 0.00.[30]

In patients with aHUS, CKD, and long disease duration (C08-003 trial) at 2 years of eculizumab treatment, 95% and 90% of patients achieved TMA event-free status and hematological normalisation, respectively. Furthermore, the TMA intervention rate reduced from 0.23 to 0.00 after patients were switched to eculizumab.[31]

Renal function was also assessed over a 3-year period.[34,35] The key endpoints here included a ≥25% decrease in serum creatinine, estimated glomerular filtration rate (eGFR) improvement of >15 mL/minute and a CKD improvement of ≥1 Stage. Data from the C08-002 trial showed that 50% of the patients showed a rapid response within the first few weeks; however, further improvements were also observed after several weeks (Figure 4). Patients who were enrolled in the C08-003 trial and were managed with PE/PI had normal platelet counts at baseline but showed signs of renal damage. Upon switching to eculizumab treatment, these patients showed improvements in serum creatinine,

eGFR rate and CKD Stage. The improvements were not as rapid as seen in the C08-002 trial population. However, over time, and even after 72 weeks, patients showed signs of improvement of renal function indicating that at this time point the kidney is still able to regenerate when excessive complement activation is blocked by eculizumab treatment.

Eculizumab was well-tolerated over a 2-year period. Serious adverse events (SAEs) included peritonitis, influenza, and venous sclerosis at the infusion site. Other adverse events (AEs) included headache, lymphopaenia, leukopaenia, cough, and anaemia. However, these appeared to decrease over time with treatment.[29]

The C10-004 study was a prospective study, which enrolled 44 patients.[33] Study participants had a decrease in platelet count and an increased LDH.[33] Serum creatinine was high (411 µM/L) and 100% of patients had an eGFR of <60 mL/minute/1.73m^2, indicating that they were at least CKD Stage 3. The primary endpoint was complete TMA response (composite endpoint: platelet count and LDH normalisation, and preservation of kidney function [<25% increase in serum creatinine from baseline]). During the 26 weeks of eculizumab treatment 73% of the patients achieved complete TMA response, 88% achieved hematological normalisation (normalisation of LDH and platelet count), and 98% showed normalisation of platelet counts.[33] Assessment of renal function showed a mean change in eGFR of 29.3 mL/minute at 26 weeks.[33] This improvement in renal function is clinically relevant since it will allow most patients to discontinue dialysis. This is supported by the study results where 83% of patients on dialysis at baseline could discontinue dialysis.[33] AEs were consistent with the other eculizumab studies; however, two patients developed meningococcal infection.[33] One patient recovered and withdrew from the study, while the other patient recovered but continued with the trial and eculizumab treatment. There were no deaths in the study.

The eculizumab dosing schedule was 900 mg every week, as an induction phase for 4 consecutive weeks, followed by 1,200 mg every 2 weeks for the maintenance phase.[29,36] As patients on eculizumab treatment are more prone to develop meningitis, it is recommended that a meningococcal vaccination is given before commencing eculizumab treatment.[36]

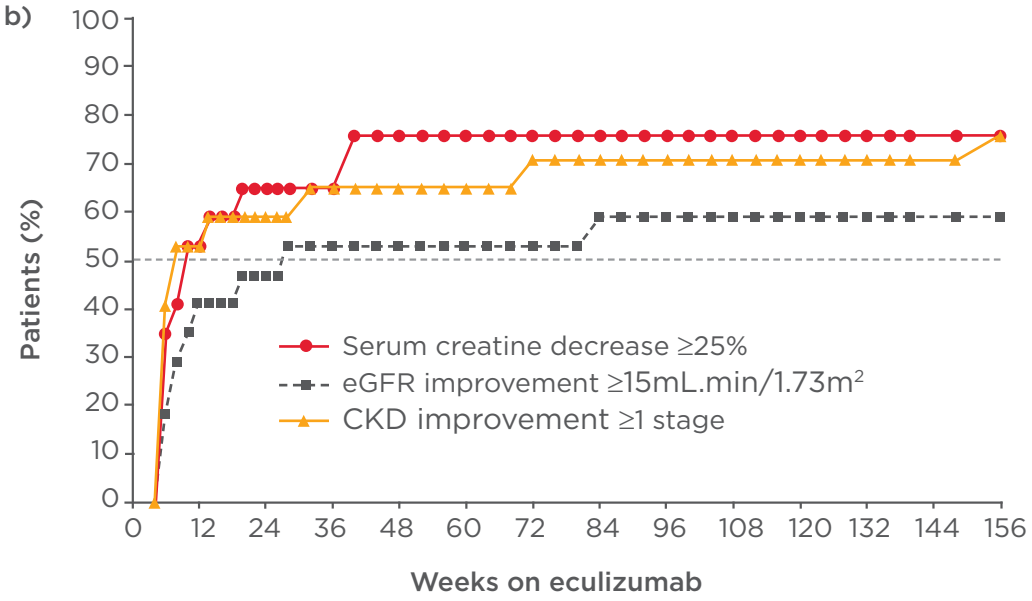

Figure 4: Cumulative percentages of patients achieving renal outcomes in patients with aHUS and progressing TMA (C08-002 trial; n=17).
aHUS: atypical hemolytic-uraemic syndrome; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; TMA: thrombotic microangiopathy.
Modified from Legendre et al.[29,35]

If eculizumab treatment is to be initiated immediately, then meningococcal vaccination can be administered with antibiotics for 2 weeks to allow activation of the vaccine. Prof Feldkamp's recommendation was that two vaccinations be administered to patients who are about to commence eculizumab treatment to ensure protection against all strains of meningococci (one being the recently approved Bexsero, active against the B strain, which is the most prevalent strain in Europe).

In conclusion, eculizumab has been prospectively evaluated for efficacy and safety in 100 aHUS patients. The three studies presented here included a broad spectrum of patients (patients with long and short disease duration managed with and without plasma exchange; patients who had undergone transplant or were on dialysis). All studies, including the latest (C10-004) and the two pivotal studies that led to the approval of eculizumab, confirm the safety and efficacy of eculizumab for the treatment of aHUS.

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