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Artículo de revisión

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# Atypical Hemolytic Uremic Syndrome, literature revision and consensus document. Diagnosis and treatment

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Todos los autores son miembros del Grupo Colombiano de Interés en SHUa y enfermedades del complemento.

**Summary**

Atypical Hemolytic Uremic Syndrome is an ultra-orphan disease, more than 50% of patients die, need renal replacement therapy or have permanent renal failure within the first year of diagnostic. With current supportive care 9-15% of aHUS patients die within 1 year following a clinical manifestation of aHUS. Severe consequences of this disease reinforce the early diagnostic and treatment importance. Clinical manifestations of this disease include the classic triad of microangiopatic anemia, thrombocytopenia and end organ damage where the renal failure is the most common manifestation, although not the only one as neurological, cardiac and gastrointestinal complications are also apparent.

Mutations on the complement system regulating proteins are recognized as the cause of this syndrome; however they are not identified in all patients as new mutations are continuously being identified. It has a high rate post-transplantation graft loss in 60% of the cases. Most known therapy for this disease, considered as the first line therapy was plasmapheresis; however it shows very poor results. Since 2011 we have a recombinant monoclonal antibody targeted to the complement component C5 (eculizumab), the only approved for the treatment of aHUS, which has proven to significantly improve the disease prognosis and progression, and is considered the first line therapy.

**Key words:** Atypical Hemolytic Uremic Syndrome, Complement. Thrombotic microangiopathy. Plasmapheresis. Eculizumab. Renal transplant

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Síndrome hemolítico urémico atípico, revisión de la literatura y documento de consenso. Enfoque diagnóstico y tratamiento

**Resumen**

El Síndrome Hemolítico Urémico atípico (SHUa) es una enfermedad ultra-huérfana; más del 50% de los pacientes muere, necesita terapia de remplazo renal o sufre insuficiencia renal terminal dentro del primer año de diagnóstico. Con el tratamiento de soporte actual (plasmaféresis o infusión deplasma) 9-15% de los pacientes de SHUa mueren dentro del lapso de 1 año, después de una manifestación clínica de hemólisis. Las consecuencias severas de esta enfermedad refuerzan la importancia del diagnóstico y tratamiento temprano. Las manifestaciones clínicas incluyen la triada clásica de anemia microangiopática, trombocitopenia y daño a otros órganos, donde la insuficiencia renal es la manifestación más común, frecuentemente asociada a otras complicaciones tales como neurológicas, cardíacas y gastrointestinales.

Las mutaciones en las proteínas reguladoras del sistema del complemento son reconocidas como las causas de este síndrome; sin embargo, no se identifican en todos los pacientes con diagnóstico de SHUa. Existe una alta tasa de pérdida del injerto postrasplante renal, en aproximadamente 60% de los casos.La plasmaféresis, considerada como terapia de primera línea, no ha demostrado resultados satisfactorios a largo plazo. Desde el año 2011 está disponible en Colombia un anticuerpo monoclonal recombinante dirigido contra el complemento a nivel C5 (eculizumab), medicamento único aprobado para el tratamiento del SHUa. Este tratamiento ha demostrado mejorar, de manera significativa, el pronóstico y la progresión de la enfermedad, y es considerado la primera línea de terapia hoy en día.

**Palabras clave:** Síndrome hemolitico uremico atipico. Complemento. Microangiopatía trombótica. Plasmaferesis. Eculizumab. Transplante renal.

## Introduction

Thrombotic microangiopathy (TMA), has been commonly classified as thrombotic thrombocytopenic purpura (TTP) and haemolytic uremic syndrome (HUS) commonly described by Symmers in 1952; they are defined by the organs involved during clinical presentation; kidney disorder prevails in HUS while a compromised central nervous system is prevalent in TTP. At the same time, the HUS has been divided into 2 types historically; typical HUS, associated with diarrhea and (aHUS) atypical not associated with diarrhea.

Based on the advances in research and the possibility of different treatments according to each entity, making a more accurate diagnosis is not only possible but also necessary in order to differentiate between TTP/HUS/ and aHUS. The discovery of the severe deficiency of ADAMTS-13as a result of TTP and some mutations in the complement system in the case of aHUS, and E. coli identification invasive integer as STEC HUS, suggest that the treatment of these entities must be different and addressed to theirspecific cause. It should be taken into account as an independent manifestation, patients with aHUS can also have diarrhea; therefore, terms such as HUS with positive or negative diarrhea are no longer used andshould be replaced by aHUS vs. STEC HUS.

aHUS is considered as an ultra-rare disease , with a population prevalence of 3.3 patients per million inhabitants year, showing a devastating behavior. It is progressive and potentially fatal because systemic activation is not controlled by the complement system [1-6]. Nine to fifteen percent of the patients die after the first year of TMA manifestation, and up to 33% of patients with aHUS progress to stage 5 chronic kidney disease (CKD) (in pre-eculizumab)2. Although, the kidney is the most frequently damaged organup to 63% of patients with HUS present with other complications and potentially fatal organ damage, which include neurological gastrointestinal and cardiovascular complications[1,6,8-12]. Those patients with aHUS who survive to the initial clinical manifestation, experience frequently a significant deterioration in the quality of life and are at risk for additional morbidities and premature death [1,2,6, 13].

In order to have an updated document for diagnosis, identification and treatment of patients with aHUS in our country, there were two face-to-face meetings conducted by a group of interested resear-

chers. Topics to be addressed includedfour different groupings (pathophysiology and diagnosis, genetic mutations, treatment and renal transplantation) were divided. The researchers collected material and some documents were shared and analyzed with the entire group,then recommendations were made for each area of interest. This document has the main findings and recommendations determined from those meetings and working groups.

## Search strategy

The search of available literature for the achievement of this work was carried out with the following term MESH "atypical Hemolytic Uremic Syndrome". It was not limited by age, language, study design, or year of publication until December 31st, 2013. Data bases such as MEDLINE, TripData Base, EMBASE, Google Scholar were consulted.

Eligibility of studies: must include original articles, regardless of : size of sample or follow-up period and was not limited by year of publication, language, or type of study. These articles, must also Include reports of cases, retrospective series and publications in academic congresses. From 181 items found, only 166 were analyzed (English and law), choosing the 57 most relevant references.

## Pathophysiology and aHUS diagnostic approach

### Pathophysiology

To understand the pathophysiology of this disease is necessary to start by understanding the complement system, and its role in the generation of the disease and clinical manifestations as well.

Complement components are produced by the liver, these ones circulate in the plasma in an inactive form and they are activated by three pathways: Classical pathway, Lectin pathway and the Alternative pathway. We shall briefly describe each one of them, clarifying that the disorder is in the regulation of the alternate route which induces to aHUS clinical manifestation .

Due to the recognition of pathogens or alterations on cell surface, the antigen and antibody form a complex with the subsequent bind C1 starting the classical pathway of the complement . The lecitin pathway is activated by the bind of lecitin and mannose residues. The two tracks converge in the excision of C4, forming C3 convertase (C4b/C2a), responsible for the division of C3 into C3a and C3b, inducing the activation of the terminal path.

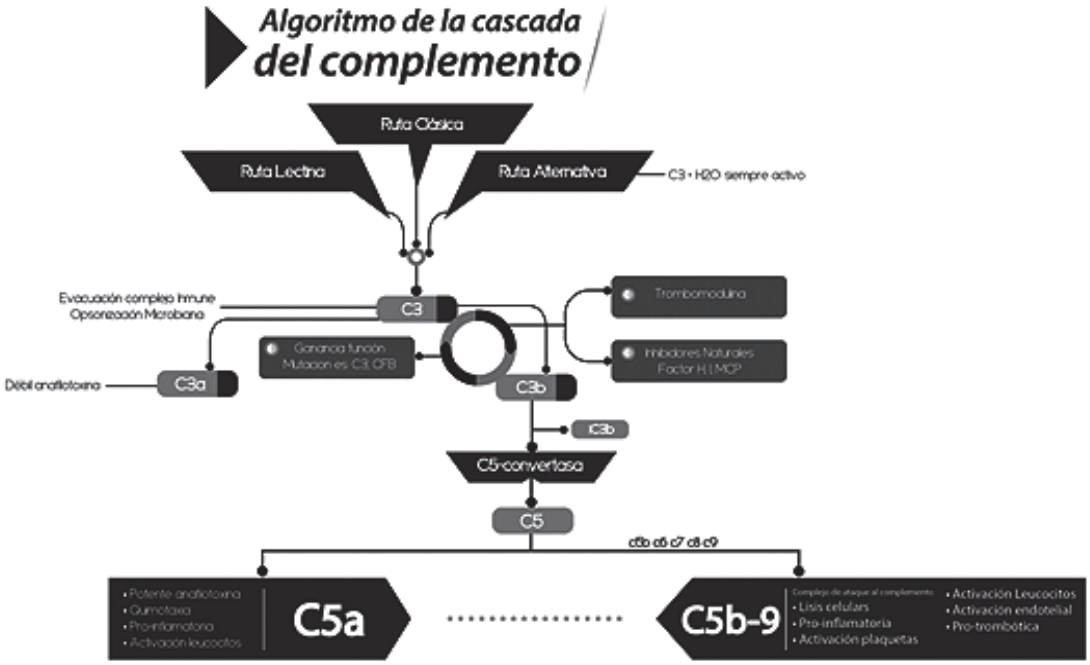
By thespontaneous C3 activation in a process known as "tickover" ,the alternative pathway is activeconstantly. This process allows complement system to be "activated" and respond to trauma and infection quickly. The alternative pathway is quickly amplified by the complement protein amplifiers, such as endotoxins, additional immunoglobulins (Ig) and polysaccharides, which imply the involvement of the system properdin factor (B and D, and properdin P). In the alternate pathway, the C3 convertase is formed by C3B/BB and cleavs C3, resulting in a positive feedback loop, amplifying complement activation through the other routes.

In order to produce C3b and activate the final track in the complement system, the three paths must converge. C3b plays a central role in the complementsystem because it can coat cell surfaces and function as an opsonin on the walls of microorganisms. In addition, C3bbinds to C3 convertase to create C5 convertase (C4b/c2a/c3b and c3b/BB/c3b), and splits C5 intoC5a and C5b.

In this process, C3a and C5a which are chemotactic leukocytes and platelets and activate the path of coagulation and participate in endothelial activation. C5b starts the final track of the complement by joining C6-C9 to form the complex attack to the membrane (MAC) on cellssurface . Finally, as it is said above, C3b can join with the factor B and the cofactor D and produce the C3 convertase alternates that divides more C3 to C3b, creating an amplification.

The assemblage of the complement mechanism is firmly controlled by inhibitory proteins located in the membranes of host cells, whose objective is to protect them from an inadequate cell activation and lysis. This process allows the achievement of homeostasis, with an effective destruction of the

Figure 1.
Cascada del complemento.




foreign organisms while preventing damage to the ownhost.The regulatory mechanisms are:

1. Factor I (IFC): serine protease that performs C3b fragmentation transforming it into inactive C3b.
2. Factor H (FCF): recognizes C3b on cell surface through the C-terminal end, it is cofactoractivity for CFI through the N-terminal cofactor and favors the dissociation of C3 convertase (accelerating deterioration) to C3B/BB.

**The membrane cofactor protein (MCP):** it is a transmembrane protein that acts as a cofactor of Factor I, perform the division of C3b and C4b deposited on the surface of the host cell. It is composed by 4 areas SCRs extracellular Sushi N-terminal, a transmembrane domain and a cytoplasmic tail C-terminal. The SCRs Sushi areas 3 and 4 are responsible for complement system regulation

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Trombomodulina (THBD) is a protein with an anticoagulant function that is involved in the generation of the carboxipeptidasa inhibitor (B) of the fibrinolysis mediated by thrombin, which cleaved C3a and C5a. THBD bindswith C3b accelerating its inactivation by Factor I in the presence of H factor

**The deterioration accelerating factor (DAF/CD55):** is a glycoprotein anchored to phosphatidylinositol that prevents the formation of C3B/BB and accelerates its destruction.

**Protectina or CD59:** it is a glycoprotein anchored to phosphatidylinositol which prevents the union and polymerization of C5B-C8 to C9 in order to form the MAC.

## Complement dysregulation

aHUS is considered as a disease of the complementsystem[1]. The alternate path is always "on" and can auto-amplify its activity under conditions of trauma, infections or injury to provide an immediate immune and hematological response. In addition, influenza, pregnancy, other conditions and medical treatments, can further stimulate the activity of complement, generating a significant amplification. In healthy individuals, their own cells are protected from the activity and permanent amplification of the complement system through a set regulated of inhibitors[3,15,16] . Patients with aHUS inherently lack complement regulators (enablers and inhibitors of proteins) that protect cells and tissues; therefore, inducing the chronic effects of a hyper active complement system [1,3,14,15].

Abnormal activity of the complementsystem in patients with aHUS and non controlled amplification as a result of the loss of regulatory proteins of the complement are reported. In fact, complementactivity is about 4 to 6 times higher in patients with aHUS. This permanent activation happens in tissue damage through different mechanisms: it alters the physiological trombo-resistent phenotype of endothelial cells, it increases the deposits of sublithicquantities of MAC, it increases the exocytosis of the P-selectin and exposure to the von Willebrand factor (vWF), due to the expression Weibel Palade bodies increases during activation and endothelial damage. In addition, it increases the expression of the tissue factor, causes the loss of the anticoagulant surface of the Heparan sulfate proteoglycans, alters the cytoskeleton with cellular retraction and exposure of the extracellular matrix procoagulant, increases the release of prostanoids, leukotrienes and cytokines by increasing the recruitment of leukocytes and the activation and transendothelial migration.

C3B and C9 deposits also increase on the platelet surface similar to CD 40L and P-selectin, which are placeholders for the granules activation and the secretion, leading the activation and premature platelet aggregation. If this process does not stop, it becomes a vicious circle that induces endothelial damage and microvascular thrombosis secondary to inflammation and continuous activation of the complement. Understanding the role of the supplement, aHUSis considered as the prototype of the disorder because of its lack of regulation and the explanation related to the diversity and aggressiveness of the clinical manifestations, as well as the component of chronic disease with its implications of morbidity and premature mortality.

Complement system proteinsdysregulation and its consequent activation, generate cellular damage at endothelial level favoring an inflammatory status, platelet aggregation and vascular stenosis. This stenosis is manifested by the presence of microthrombi in systemic microcirculation. It is important to highlight that the main mechanism of the vascular stenosis in this entity is secondary to endothelial damage, which induces fibrin clots rich in TTP hallmarks of hight platelets count due to extensivemultimers circulating vWF.

## Pathology

TMA (thrombotic microangiopathy) means histological damage of arterioles and capillaries, characterized by vessel wall thickening and inflammation, detachment of endothelial cells, subendothelial elongation caused by deposits of protein and the material of the cellular lysis and the presence of thrombi platelet that occlude the vascular spaces. Carrying out a biopsy for TMA diagnosisis not necessary. By the decrease in the platelet count or thrombocytopenia, TMA can be identified, and the presence of hemolysis (measured by the increase in the levels of LDH or by undetectable levels of haptoglobin) as well, the presence ofschistocytes in the peripheral blood smear (FSP). TMA can be presented in systemic way and patients with aHUS often showa non-renal organic lesion.

## Clinical presentation

Data relating to aHUS clinical presentation is limited due to the number of patients. Cases from the neonatal period are reported, this disease affects children and adults. Between male and female the distribution is equitable in childhood, but tends to predominate in women in adult life. The infectious events and upper respiratory tract infections or gastroenteritis are triggers of the disease in approximately half of the patients. Although the association with diarrhea was presented in the STEC HUS, up to 24% of cases of aHUS presents diarrhea history. It is not clear whether the event of diarrhea is a trigger or a result of the TMA. 21% of women have their first manifestation during gestation, the majority of them (79%) in the postpartum period[28].

Because of the symptoms are unspecific: pallor, hyporexia, vomiting, fatigue, drowsiness, commitment of urinary volumes, edemas, a complete medical history is relevant. Patients may present marked hypertension and even reversible posterior encephalopathy and heart failure. In fact, clinical studies involving 67 patients sampled have shown that 75%, 60%, 40%, 34% and 46% of patients had cardiovascular symptoms, gastrointestinal, neurological, thrombus extra-renal and pulmonary complications, respectively[50].

## Paraclinical

aHUSisclinically characterized by microangiopathic hemolytic anemia (hemoglobin, lactatedehydrogenase (LDH) high, haptoglobinloworundetectable,schistocytesin FSP, Coombs negative test), thrombocytopenia (plateletcount<150000 or a rapid decline) and acutekidneyinjury (hematuria, proteinuria orreducedkidneyfunction). It must be taken into account that aHUS is a systemic disease that affects any organ endothelium

## aHUS diagnosis

With clinical suspicion before TMA presentation or a previous history starts the first step in diagnosis. TMA can be defined as hematological parameters, with diagnostic tests to confirm the platelet consumption expressed by thrombocytopenia (platelet count <150 x109/L) or the decrease in platelet counts (defined as a decrease >25%). In addition, the platelet activation, reported evidence of hemolysis. Hemolysis can be identified due toLDH elevation above the normal limit secondary to the fragmentation of red blood cells, presence ofschistocytes in the FSP, low hemoglobin levels or undetectable levels of haptoglobin[19].

- Most of the aHUS patients show a triad composed by:
- 1. microangiopathyhemolysis
- 2. Plateletalteration
- 3. Target organdamage:
- Renal impairment, organ damage recognized with greater frequency in patients with aHUS: decline of glomerular filtration rates with or without alteration of the urinary volume or need of renal replacement therapy.
- analysis of urine suggestive of glomerular pathology (proteinuria or hematuria)abnormalities
- - Other symptoms of damage or organ engagement that patients with aHUs may present [2,12,20]:
- (20-48%) Neurological: seizures, confusion, irritability, diplopia, cortical blindness, hemiparesis, stupor, coma, among others.
- gastrointestinal (37%): diarrhea (30%) and other symptoms such as colitis, nausea, vomiting, or abdominal pain
- Cardiovascular Disease (3-5%): acute myocardial infarction, heart failure, sudden death, HTA and peripheral ischemic vasculopathy.

  Failure of multiple organs (5%): pancreatitis, SNC, gastrointestinal hemorrhage, alveolar hemorrhage and liver involvement.
- Alterations of the vascular permeability: ascites, pulmonary edema, cerebral edema and pleural hemorrhage

## TMA secondary causes assessment or aHUS coexisting conditions

There are specific conditions that have increased the possibility of coexistenceor aHUS or TTP manifestation due to the complement system activation and amplification.aHUSis usually identified because of a coexisting condition; based on the International Register aHUS/TTPthroughthe evidence corresponding to the observation of 70% of patients with aHUS approximatelyidentified with the coexistence of other diseases or conditions[2]. Theconditionsthatfrequentlycoexistwithahusare malignant arterial hypertension induced by drugs, LES and pregnancy. The presence of these conditions does not rule out the aHUS. The history of recurrent TMA or family history should generate suspicion of aHUS and disturbances of the regulators of the complement.

There are several conditions that may also occur with the TMA, these include

- Status of pregnancy or postpartum: HELLP syndrome.
- autoimmune diseases: systemic lupus erythematosus (SLE), antiphospholipid syndrome (APS) and scleroderma.
- HIV infection, H1N1 or pneumococcus.
- Malignant arterial hypertension.
- glomerulopathies.
- neoplasms.
- methylmalonicacidemiawithhomocystinuria.
- bonemarrowtransplant.
- medications: quinine, mitomycin C, gemcitabine and cisplatin, radiationwithiodine, interferon, clopidogrel, mitomycin, calcineurininhibitors, sirolimus, valacyclovir, oral contraceptives, inhibitors of vascular endothelialgrowth factor (VEGF) and tyrosinekinase (sunitinib, imatinib and dasatinib).

**Drugsinduced TMA (kidney transplant)**: There are certaincategories of drugsinducedTMAthrough a directtoxicityto endothelialcells [21,22]. The Calcineurin inhibitors and some chemotherapeutic agents can induce endothelial activation and cause TMA self-limited (drugs induced TMA) but can also be the trigger of aHUS. The history of transplant anduse of calcineurin inhibitors are found in 24% of patients with aHUSin coexisting conditions[2]. If the suspension of the medication, LDH nor the platelet count are not normalized, it should be considered that the patient has TMA from another source and therefore high suspicion of aHUS.

- Malignant or severe hypertension: Malignant hypertension may induce aHUS. There is evidence that malignant or severe hypertension can induce platelet activation and endothelial damage. Approximately 30% of patients with malignant hypertension presented evidence of TMA. The International Registration of aHUS/TTP reported an association between aHUS and malignant hypertension as a coexisting disease[2]. In these patients with malignant hypertension and coexistence with aHUS there is evidence of mutations in the proteins of the complement [2].

**LES:** SHUa can be diagnosed in patients with SLE2. In this case, the complement is active, inducing injury, cellular inflammation and generating risk of TMA development. TMA has been reported in 1-4% of patients with SLE. Autopsy reports show 14% prevalence of TMA in these patients, suggesting that TMA is ignored in this condition . The patients with SLE and TMA or ERCstage 5 are at risk of death 3 to 4 times more than patients with SLE without TMA or kidney failure

**Pregnancy or postpartum period:** aHUS is MAT cause in the third trimester of pregnancy or in postpartum period[2]. Pregnancy is associated with a systemic activation of the complement to protect both mother and fetus from possible infections. In fact, it has been shown that the levels of proteins anaphylatoxin C3a, C4a and C5a are higher in pregnant women than non-pregnant women, near 2, 4 and 3 times more, respectively[26]. Pregnancy precedes the clinical presentation of aHUS in 10 per cent of women and can unmask aHUS. Based on International Registry aHUS/TTP reports, in 86% of these pregnant patients with aHUSis evident abnormalities in the complement 2. The prognosis is poor, with more

than two thirds of the patients attaining ERC stage 5 mostly, in the next month after the beginning of the manifestation

In addition, pregnant patients with a mutation can also present in HELLP syndrome or severe preeclampsia by underlying of the complement factors' regulators.

tests application in order to evaluate all above described depends on the clinical suspicion according to the information provided by the patient or according to patient age group.

### aHUS diagnosis based on the exclusion of other TMA etiologies

Taking into account, the similarity of the TMA multisystem involvement, it is important to rule out the presence of TTP and STEC-HUS in patient with clinical thrombotic microangiopathy, in order to confirm aHUS diagnosis. The possibility of aHUS or secondary thrombotic microangiopathy should be considered in patients with ADAMST13 >5% activity and a negative STEC test.

### Assessment of ADAMTS-13 activity

Due to aHUSclinical manifestations may overlap with the ones related to thrombotic thrombocytopenic purpura (TTP), a differential diagnosis must be conducted. Previously, it was considered thatTTP diagnosis was based on the presence of neurological alterations, while the diagnosis of aHUS was based on the presence of kidney involvement. However, 47% of patients with aHUS have neurological deterioration. Therefore, the differentiation of these diseases should not be based solely on the clinical manifestations. At this point, it is important to the measurement of ADAMTS-13activity. TMA development in the TTP is due to a severe deficiency of ADAMTS-13 activity (<5-10%). The severe decrease of activity of ADAMTS-13<5% confirms the TTP diagnosis and discards aHUS. A test in serum before start therapeutic plasmapheresis or plasma infusion (PF/PI)should be applied to ensure an accurate measurement of ADAMTS-13 activity since the plasma used in these therapies have ADAMTS-13 and alter the results.

In those cases whena blood sample to assess ADAMTS-13 activity has been taken, after starting of therapy with PF/IP, or when there is no availability of the test a diagnostic approach based on the result of platelet count and creatinine serum may be carried out. In this regard, four studies have suggested that a creatinine serum level greater than 1.69 mg/dL or a platelet count greater than 30 x 109/L may exclude the diagnosis of severe deficiency of ADAMTS-13 [31-34]. In this way, the characteristics of the laboratories can differentiate between aHUS and severe deficiency of ADAMTS-13, i.e. TTP

The SHU-STEC is caused by a shiga toxin produced by Escherichia coli and Shigella dysenteriae, and due to the manifestation of the infection caused by these bacteria is diarrhea; this disease was formerly known as HUS-D (D, diarrhea). 30% of patients with aHUS presented diarrhea, but some patients with STEC-HUS do not, therefore; this designation based on the presence or absence of this symptom is incorrect. To diagnosis STEC-HUS,this toxin must be present or a positive culture of STEC must be detected, so that all patients who have symptoms of TMA must be screened.

If the patient presents a table of TMA without diarrhea or if patient have diarrhea with any of the following the clinical suspicion for aHUS should be greater:

- Less than 6 months or more than 5 years of age.
- Recurring HUS.
- Suspicion of prior HUS.
- Prior TMA is not explained.
- Post transplant TMA .

  TMA associated with pregnancy (postpartum).
- HUS familiar non- synchronous.
- Pesrsistently low C3

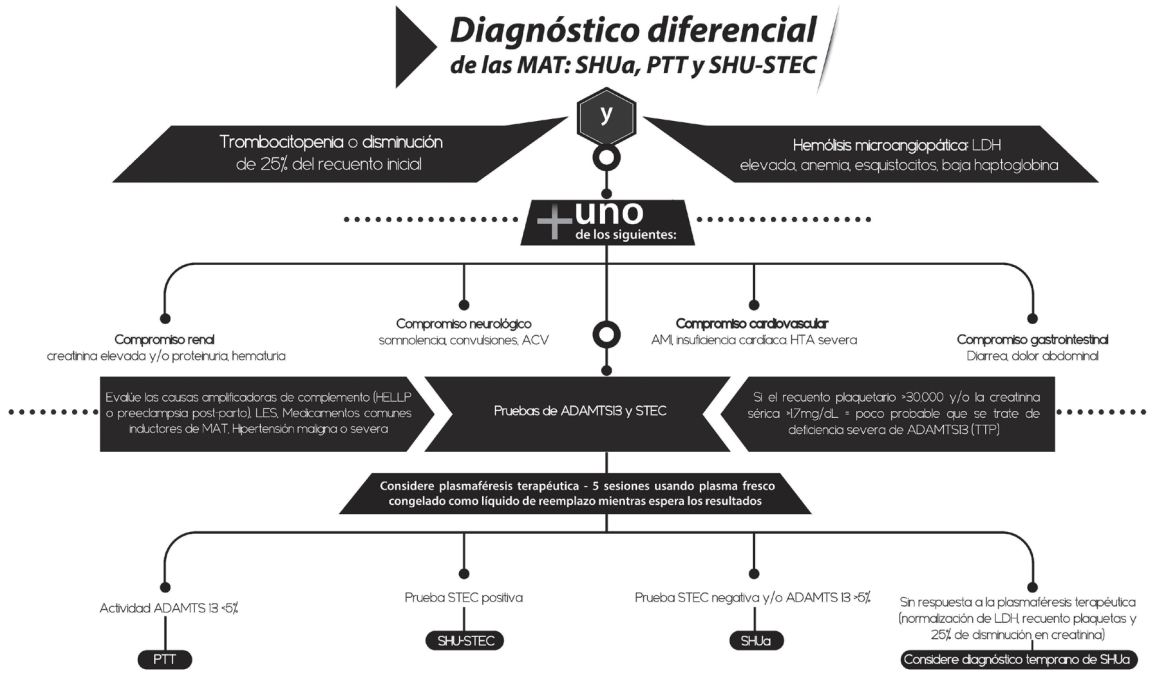
## Colombian group of consensus for a proposal based on diagnosis of aHUS

### Genetics tests role.

The genetics of complement system has contributed to our knowledge about the aHUS2. 40-60% of patients approximately with aHUS develop specific mutations in complement genes and these mutations cause the complement dysregulation 2 of the alternative pathway, according to recent studies. This dysregulation can be produced both by a decrease in the activity of the regulatory proteins, and by the abnormally high activity of C3-convertasas, i.e. mutations with gain-of-function and loss of function genes. The mutations described until this moment, involve the factor H (20-30%), MCP (5-15%), factor I (4-10%), C3 (2-10%), factor B (1-4%) and THBP (3-5%) and up to 12% of cases, have identified more than a mutation in the plugin[2,34]. The penetration is incomplete, and approximately 50% of the mutation carriers factor H (CHF) or MCP do not develop the disease. The reasons are not clear, there are genetic variants that influence this fact, haplotypes of risk are not determinant for the disease occurrence and environmental triggers associated with pregnancy, viral infections, cancer, organ transplantation and certain medications[34].

| RecomendationsaboutaHUS diagnosis |
|---|
| One should recognize early presence of TMA, based on a clinical evaluation and the presence of: |
| a. Microangiopathic haemolytic anemia. |
| b. Thrombocytopenia or decrease of platelet count in 25%. |
| c. Injury of white body, renal, cardiovascular, neurological, etc. (remember that in the aHUS kidney damage in most of the cases associated with alteration in the TFG, requirement of renal support therapy or presence of hematuria or proteinuria in the urinalysis is presented. |
| 2. To evaluate conditions amplifiers of the complement as triggers (pregnancy, LES, transplant, cancer, medications, infections) |
| 3. Provided that they are always available, conduct confirmatory testing of STEC-HUS (crops, PCR or ELISA) and TTP (deficiency of ADAMTS-13 activity) for all patients with TMA. |
| In case of non-availability to perform ADAMTS-13 activity: |
| a. One should suspect that TMA secondary to severe deficiency of ADAMTS-13 (activity less than 5%) when you have severe thrombocytopenia (less than 30,000 platelets) or non severe renal compromise (serum creatinine less than 1.7mg/dl) are evident. |
| Suspect TMA by aHUS in patient if there is no hematological normalization or decrease by 25% of the serum levels of creatinine after 5 sessions of plasmapheresis. |
| 5. Always suspect aHUS in patients who present : |
| a. Recurrent episodes of TMA |
| b. Have a family history of aHUS |
| c. Child under 6 months with TMA |
| d. There is a presence of TMA diarrheal without disease. |
| e. TMA associated with low complement under C3 especially |
| 6. Molecular tests for detecting genetic abnormalities of complement factors are desirable but are not required for the diagnosis of aHUS |

Figura 2.




The first family case related to twin monocygotic study was reported in 1965. In 1973 the decrease of the serum C3 levels in 5 patients with severe HUS was reported. The Association of aHUS with low levels of FCF in plasma was reported for the first time in 1981; however, it was only until 1998 when Warwicker et al., studied 3 families with aHUS and established the relationship between the aHUS and locus that regulates the activation of the complement system. A heterozygous mutation in SCR 202 was found at the location of the chromosome 1q32 where the genes CFH and MCP 2,7 are located; Subsequently, multiple mutations in the genes associated with CHF (CFHR1, CFHR2, CFHR3, CFHR4, CFHR5) that are close in location and share many of its functional properties were demonstrated. There have been reported cases of hybrid genes CFH/CFHR4; these show a normal activity in its liquid phase but lost its role as regulator of the complement on cell surface. The C3 levels are diminished in 30-50% of patients with heterozygous mutation of CFH[2,7].

In 2003, Richards et al., reported the first MCP mutation, 2 mutations in 3 families, a deletion 6bp and c.822 T>C, causing this last a change of serine by proline, inducing the decline of the union of C3bin 2003. Subsequently, more than 40 different mutations in this protein2 which have been classified as type I (75%) in which the expression on the cell surface is diminished, and TYPE II (25%) with a normal expression, but with a decrease of the regulatory activity of the complement (7) have been identified. In most of the cases, the C3 levels are normal, however, Italian registry reported a decrease of 27% of patients in C3 level, suggesting that these patients had a coexisting mutation that explains the activation of the complement in the liquid phase . The MCP mutations are more frequent in children than in adults and in transplanted patients. This mu-

tation has better prognosis compared with the other, with recurrence rate of 20% after kidney transplant, attributing this behavior to the fact that the cells of the transplanted kidney do not have the genetic defect of the patient[2].

For first time in 2004, IFC mutations in 3 patients were described; In this moment, more than 40 mutations all of them heterozygotes have been described. These mutations produce an alteration in the secretion of the protein or an alteration in the activity of the cofactor that alters the degradation of C3b/4b in the liquid phase and on cell surfaces. Decrease in C3 serum concentrations was presented in 20-30% of the patients and a diminished serum in a third of the patients. The recidivism rate after kidney transplant has been described in 45-80% of cases[2,7,36].

Goicoechea of Jorge and Roumenina reported 4 mutations in the CFB heterozygote; In 2007 and 2009, these mutations are associated to a functional profit, which allows an excessive bind to C3b inducing greater stability and activity of C3 convertase. These mutations are associated with very low levels of C3 and the rate of recurrence is 100% (2) after transplant .

C3 is considered the cornerstone of the complement system; the first mutations reported are located in alpha and beta chains; Frémeaux-Bacchi reported 9 C3 mutations in14 patients of 11 families, including a Mutation P-R570Win 2008,. Some of them diminish the capacity of C3 to join MCP, generating a mutant convertase resistant to division by the CFI. Like in other factors, different mutations of this proteín are discovered (2,7). In 70-80% of patients C3 levels in plasma are low and the risk of recurrence after transplant is 40-70%[2].

those mutations that have been described most recently are THBD; it was demonstrated in an italian cohort of 13 patients sampled. The THBD binds C3b and the FCF acceleratomg C3b per CFI inactivation. In cases of mutation, their ability to break C3b is reduced. The C3 levels are lower in half of the patients and the risk of recurrence disease after transplant has not been determined (34),

CFH functional alterations acquired due to antibodies directed against the C-terminal region were described in 2006. The IgG against the CFH SCR19 and 20 inhibit the union of CHF to C3b and increase the concentrations on the cell surfaces (2,37). 90% of patients with antibody anti-CFH have absolute deficiency of CFHR1 and CFHR3, suggesting that this deletion plays a pathogenic role in the development of these antibodies. Patients may also present mutations in other components of the complement and in 40-60% of the cases C3 levels have decreased up to 10 % of the cases of aHUS (2 ) as it has been reported

10-12% of the patients showed mutation in more than a genetic component; this means that a match of different genetic factors is decisive for the development of aHUS (theory of multiple hits).

Due to wide variety of mutations and the incomplete self penetration, the symptoms and the age of initiation are different, even in patients within the same family and calculated risk of the disease based on who suffer from aHUS, then it is difficult to determine. Based on the Pediatric cohort of France and age or early onset in patients with mutation in the FCE (an average of 6 months, 3 days to 3.6 years) was observed and the CFI (an average of 2 months and 1 day to 3.8 years) while, the start in children older than 1 year was more frequent in the cases of MCP (2) mutations. The antibodies anti CHF are more frequent between the 7 and 11 years

A measurement of serum levels and the genetic sequence in reference laboratories (Table 1) must be performed. Blood samples should be taken prior to the start of treatment with PF/IP, excluding the expression of MCP in the peripheral leukocytes, which is not affected by this therapy. In the case of the homozygous mutations, all patients have decreased at all levels of factor H (<1% -normal 70-130%), C3 (<40-170mg/dL - normal 660-1250mg/dL), factor B (17-70mg/L - normal 90-320mg/L), and CH50 (<10-24%- normal 70-130). In patients with heterozygous mutations normal or low levels of the following may be found, factor H (30-55%), C3 (240 to 834 mg/dL), factor B (55 to 250 mg/L), and CH50 (59 to 124%) .

In all patients with any aHUS clinical suspicion in the levels C3 and C4 in serum must be measured.

At the first episode or within 3 years after its manifestation, more than 70% of the patients with CFH, CFI, C3 or THBD mutations or with antibodies anti FCF develop CKD or die. The patients with MCP mutations have more recurrences; however, they have a better 3 years after prognosis than all other groups6. Mortality is higher in children than in adults (6.7% vs. 0.8% at 1 year p=0.02) but the progression to ERC after the first episode is more frequent in adults (46% vs. 16%, p<0.001)[34].

The genetic and complement tests in serum are not required to make the aHUS diagnosis. The reason for this, is that 30% to 50% of patients with aHUS approximately do not show an identifiable mutation. Although the genetic defects in the regulatory proteins of the alternative pathway of the complement are a direct cause of aHUS, the current diagnostic algorithm does not require genetic testing as a confirmation for aHUS

### aHUS Genetic classification approach

It is important to take into account that the identification of the genetic mutation not only can be related to aHUS cause but it is also considered a risk factor for the disease. The specific role in the determination of each one of the abnormalities of the complement by using the sequencing is still uncertain; however, with the current information, in those patients with aHUS in which mutations have been identified of the plug-in, the diagnosis can be reaffirmed, provide genetic counseling to the families of those who suffer this disease, to predict the risk of recidivism, assessing the prognosis in relation with renal survival and general mortality, evaluate the course after renal transplant, potentially determine the duration of the treatment and what treatment choice to prevent a relapse after transplant (Table 2)[2]. These factors also plays a significant role in the selection of the living donor who is a relative.

Recommendations about the aHUS genetic study

It should be mandatory tests prior to the kidney transplant the screening for mutations of all the genes associated with aHUS; CFH, CFI, MCP, C3, CFB, and THBD,. In the rest of cases is desirable but not mandatory. The measurement of serum levels and the genetic sequence must be performed in reference laboratories experienced in this process.

## Treatment

Plasmapheresis (PF) was the only therapeutic alternative for this disease for many years; however, the results related to 5-10 years are still unfavorable

Table 1.

Measurement table of complement components

| Diagnostic test | Treatment |
|---|---|
| C3 and C4 serum levels | Nefelometría |
| C3d serum levels | Immunoelectrophoresis (EDTA) |
| FCF and IFC serum levels | radial immunodiffusion serum |
| Anti-CFH antibody | ELISA (serum) |
| PCM expression | FACS (EDTA) |
| Screening of CFH, CFI, MCP, CE AND CFB | Sequence analysis |

adapted from Ref39.[39].

with very high rates of progression to ERC and mortality (60-80%)2. Since 2011, the eculizumab has been made available, this is a recombinant monoclonal antibody hybrid Ig2/IG4, totally humanized, directed against the component C5 of human complement. The recruitment of inflammatory cells and the activation of the complement 3 has been designed to minimize the immunogenicity [9] . The normal concentration of C5 in plasma is approximately 70µg/ml; the Eculizumab achieves the total blockade of the complement when its concentration in serum reaches 35µg/ml. After intravenous administration, the Eculizumab has a half life of approximately 11 ± 3 days, and is distributed in the vascular space

## Support Therapy: plasmapheresis therapeutic/ plasma exchange (PF/IP)

Historically and empirically, the PF/IP has been considered as a therapeutic alternative for aHUS treatment, this is after observing for more than 3 decades this treatment reduced the rates of mortality in a population of patients with HUS-TTP1. The evidence supports that the replacement of ADAMTS-13 with PF/IP could improve the results in patients with TTP . However, the role of PF/IP in aHUS is less clear. Recent evidence suggests that the PF/IP in order to adequately control the systemic and permanent activation of the complement in patients with aHUS[17] is ineffective . This is reflected in those patients who have only received treatment with PF/IP progress, with some frequency, extra-renal complications (ERC) or death13; 9-15% of the patients die and 33% progress to kidney failure within the first year of the clinical manifestation of TMA despite the management of maintenance with PF/IP in one year period [2,7].

In addition, it is known that the administration of PF/IP has reported technical complications such as bleeds, electrolytic disorders, infectious processes and infectious processes related to Vascular access; these ones are being more important in the pediatric population[1,46]. However, despite the inability of the PF/IP for the treatment and management of aHUS, traditionally the PF/IP has been part of the first line interventionist, especially in instances in which there is no availability of eculizumab or the diagnosis is not clear; considering the fact previously mentioned PF/IP can provide interim support to patients with aHUS waiting for clinic or paraclinic confirmation .

Table 2.

Clinical characteristic of patients with aHUS based on the genetic classification

| Gen | Frecuency | Starting-minimum age | | Risk of death o CK 5 a 1 year | Risk of incidence risk | Risk of postrasplante | Plasmapheris indicator |
|---|---|---|---|---|---|---|---|
| | | Children | Adults | | | | |
| CFH | 20-30% | RN | Any | 50-70% | 50% | 75-90% | Sí |
| CFI | 4-10% | RN | Any | 50% | 10-30% | 45-80% | Sí |
| MCP | 5-15% | >1año | Any | 0-6% | 70-90% | <20% | cuestionable |
| C3 | 2-10% | 7m | Any | 60% | 50% | 40-70% | Sí |
| CFB | 1-4% | 1m | Any | 50% | 100% | Cualquiera | |
| THBD | 3-5% | 6m | Rare | 50% | 30% | 1 p | Sí |
| Anti CFH | 6% | 7-11años | Any | 30-40% | 40-60% | Altos títulos | Sí (+inmunosupresor) |

Adaptado de Ref[2].

## Eculizumab management of patients with aHUS diagnosis. Efficacy and safety

Four clinical studies of eculizumab made by the industry, in patients with SHUa have been reported, the 2 studies of record C08-002 and C08-003 and two studies in progress, C10-003 and C10-00[46,45]. In addition to these studies a retrospective clinical study (C09-001 r)[6.12], was conducted. Participants in the study were all negative to the shiga toxin and had ADAMTS-13 activity of Above 5% (6.45). Participants were not required to complete prior screening nor was the identification of a genetic mutation of the complement required (6,45). Below we present a

## Prospective studies: C08-002 C08-003

study C08-002, evaluated the safety and efficacy of Eculizumab in 17 patients (adults and adolescents) with active disease progression or treatment with PF/IP[6,45]. The primary outcome was assessed as the decrease of the TMA measured by the change in platelet count. It did not require the prior identification of the complement mutation [6,45,54]. After 26 weeks platelet counts normalized in 14 of 17 patients (82%) and the hematological normalization was evident in 13 patients (76%) at the same period of observation, rising to 88% of patients at 2 and 3 years of follow-up (Tables 3 and 4)[6,45,51]. In this study, 4 of the 5 patients who were on dialysis recovered renal function and therefore the dependence on dialysis disappeared . 88% of the patients did not have a need for PF/IP during the entire study period45. An improvement was observed in the EGFR (≥15 mL/min/1.73m2) in 47% of patients (8/17) at the 26th weeks mark and in 59% (10/17) at 2 and 3 years of follow-up[45,51,54]. Sixty-five percent of patients (11/17) showed a decrease greater than 25% in the values

At 26 weeks, plasma creatinine, the percentage of patients who rose to 76% at 2 and 3 years of follow-up. Finally, the quality of life improved with the Eculizumab treatment, the change in EQ-5D was very significant at 26 weeks and remained the same for the second and third year of monitoring[45,51,54].

The change in the platelet count, the normalization and stabilization haematological or renal improvement, with the treatment with eculizumab reached regardless of the identification of a mutation of complement or a history of kidney transplant6,[45,54].

Based on study C08-003, a total of 20 patients with prolonged illness and chronic kidney failure that had received PF/IP, long-term treatment during 26 weeks with eculizumab with the option to enroll in a study of the extension (total 3 years)6,45,54 were treated. At 26 weeks, 80% of the patients were free of events of TMA (without decrease in the platelet count >25%, without PF/IP and without starting dialysis)[45,54]. As shown in tables 1 and 2, a total of 18 out of 20 patients (90%) achieved hematologic normalization within 26 weeks, which was maintained in the follow-up for 3 years,47. The indefinite treatment with Eculizumab resulted in a continued and sustained increase in the EGFR. The patients continued to improve kidney function during follow-up, as 5 per cent of the patients at 26 weeks, 15% at 62 weeks and 40% of patients at weeks 114 and 156 achieved a change in the EGFR ≥15 ml/min/1.73m$^2$[45,47,54]. All patients in treatment with Eculizumab in this study discontinued the treatment with PF/IP and no longer needed dialysis[6,45]. The patients showed clinically meaningful improvements in the quality of life (QoL), measured by Euro QoL-5D at week 26, which was maintained until the end of the study[45,47]. The change in the platelet count, the hematological normalization and stabilization or renal improvement with treatment with Eculizumab was achieved regardless of the identification of a mutation of the add-in or a history of kidney transplant[6,45]. A patient died, without being attributed to the treatment with eculizumab[47].

Tthe Eculizumab long term treatment is effective in patients with aHUS[54] as these two clinical studies show. Also a statistically significant association was found ($p<0.05$) between the time of initiation of treatment with Eculizumab and best renal outcomes measured by increase in GFR. These findings could suggest that it is important to define early start of this treatment in cases of patients with aHUS in order to attain better clinical outcomes.

## Prospective study C10-003

With this first prospective study the treatment in a pediatric patients with aHUS. was evaluated. The inclusion criteria did not require that patients needed to receive PF/IP before the start of Eculizumab, as inclusion criteria. The study evaluated the effectiveness of Eculizumab in 22 pediatric patients. Complete response was defined as the standardization of platelet levels and LDH and decrease ≥25% of the initial value of the serum creatinine taken in 2 consecutive measurements (more than 4 weeks of difference)[6,48]. Complete response was documented in14 of 22 patients (64%) at 26 weeks (Table 3)[48]. The 95% reached platelet normalization and 82% reached hematological normalization 48. 73% showed a decrease in Creatinine serum ≥25% over a period of 26 weeks of treatment and 86% of patients had improvement in the EGFR to values above 15 mL/min/1.73m2[48]. Finally, 9 of the 11 patients (82%) in renal replacement therapy suspended the dialysis treatment with eculizumab6,48. The 10 patients who were treated with PF/IP at the start of the study were suspended. This study is still in progress[6].

## Prospective study C10-004

This C10-04 study, is a clinical study in progress, designed to determine the efficacy of eculizumab, in 41 adult patients with aHUS. The full response to the TMA was defined as the normalization in the levels of platelets and LDH and a decrease >25% from the initial value in creatinine serum, in 2 consecutive measurements (more than 4 weeks apart). Patients do not need to receive PF/IP before Eculizumab treatment starts. The platelet normalization was achieved by 98% of the patients and the hematological standardization by 88%[53]. 73% of patients achieved a complete response to TMA along 26 weeks[53]. Twenty-two of 41 patients (54%) achieved an improvement in the EGFR, from the initial value, over a period of 26 weeks. Dialysis was interrupted in 83% of patients who were in this procedure at the start[53].

## Measures to eliminate the risk of infections with Neisseria meningitidis

Patients with C5 severe deficiency or, therefore, with a total blockade with medications such as Eculizumab, are at higher risk of infection by Neisseria meningitidis[57]. Therefore, all patients with HUS must be vaccinated against this bacteria before they receive the first dose. The vaccine should be administered in the course of the disease to optimize their effectiveness as soon as possible. You must use tetravalent vaccines (A, C, and W135), preferably conjugate. Patients in which starts the Eculizumab treatment before 2 weeks after the shot, should receive prophylactic antibiotics daily (e.g. oral penicillin) until 2 weeks after the vaccine administration. it must be managed a macrolide to patients allergic to penicillin. It should be taken into account that the vaccines, currently available,do not cover all the strains of N. Meningitid is including the most prevalent sero group in Europe and America, i.e. the sero group B. In addition, the uncertainty related to vaccines efficacy in immune compromised patients (e.g. those with end-stage renal disease and renal transplant patients). These concerns have led some countries, including France, to require permanent prophylaxis with antibiotics along the treatment with Eculizumab. The patients should be vaccinated once again, in accordance with the medical guides in force. It is important to note that there is also a need for vaccines against Haemophilus influenzae type b and Streptococcus pneumoniae in children treated with Eculizumab[56,57].

## Recommended dose regime –aHUS

for patient size >aHUS 18 years of age, therapy with eculizumab consists in[56]:

- 900 mg weekly during the first 4 weeks, followed by
- 1200 mg in the fifth week and then
- 1200 mg every 2 weeks thereafter.

Table 3.

Characterisitics of initial clinical prospective studies based on Eculizumab treatment data and efficacy at 26 weeks [6,45,48,53,54].

| Characteristics | C08-002 (N=17) MAT progressive active | C08-003 (N=20) SHUa prolongued | C10-003 (N=22) Prospective pediatric | C10-004 (N=41) Adult prospective |
|---|---|---|---|---|
| **Características iniciales** | | | | |
| Age, years (médium range) | 28 (17-68) | 28 (13-63) | 6.6 (6.1)a | 40.3 (15.3)a |
| Men; n (%) | 5 (29) | 8 (40) | 12 (55) | 13 (32) |
| Complement mutations antibody; n (%) | 13 (76) | 14 (70) | 11 (50) | 21 (51) |
| Time from the diagnostic to the screeing stage; month (médium range) | 9.7 (0.3-235.9) | 48.3 (0.7-285.8) | 0.56 (0.03-191.3) | 0.8 (0-311) |
| PF/IP; n(%) | 17 (100) | 20 (100) | 10 (45) | 35 (85) |
| Dialysis; n(%) | 6 (35)b | 2 (10) | 11 (50) | 24 (59) |
| Prior renal transplant; n(%) | 7 (41) | 8 (40) | 2 (9) | 9 (22) |
| Plateletes<150x109/L; n(%) | 15 (88) | 3 (15) | 22 (100) | 27 (66) |
| LDH>ULN; n(%) | 10 (59) | 4 (20) | 19 (86) | 32 (78) |
| TFGe ≤60 ml/min/1.73m2; n(%) | 17 (100) | 18 (90) | 18 (82) | 41 (100) |
| **Efficacy criteria at 26 weeks of Eculizumab treatment** | | | | |
| Complete answer to MAT; n(%) | 11 (65) | 5 (25) | 14 (64) | 30 (73) |
| Free status events TME; % | 88 | 80 | NR | NR |
| Plateletes normalization; n(%) | 14 (82) | NA | 21 (95) | 40 (98) |
| Hemotological normalization; n(%) | 13 (76) | 18 (90) | 18 (82) | 36 (88) |
| Increase TFGe ≥15 ml/min/1.73m2; n (%) | 8 (47) | 1 (5) | 19 (86) | 22 (54) |
| Decrease in serum creatinine ≥25%; % (IC 95%) | 11 (65) | 3 (15) | 16 (73) | NR |
| Change HRQL average EQ-5D (IC 95%) | 0.32 (0.24-0.39; P<0.001) | 0.10 (0.05-0.15; P<0.001) | NR | NR |

Abbreviations: OF: standard deviation; NR - not reported; ULN: normal limit higher; MAT: thrombotic microangiopathy; NA: Not applicable; HRQL: health-related quality of life

a. Average (Standard Deviation); b. A patient suspended dialysis 5 weeks before the start of treatment with eculizumab; c. Calculated on a total of 80 patients; d. Calculated on a total of 41 patients (from studies C08-002, C10-003 and C10-004) who needed dialysis to start; e. Clinically significant threshold ≥0.06. (The table does not include these notes)

Table 4.

Tratamiento a largo plazo con eculizumab (datos a 2 y 3 años)[6,47,51].

| Criterios de eficacia | C08-002 (N=17) | C08-003 (N=20) | | | | |
|---|---|---|---|---|---|---|
| | 64 semanas | 2-años[a] | 3-años[a] mediana | 62 semanas mediana | 114 semanas | 156 semanas |
| Normalización hematológica[b]; % (IC 95%) | 88 | 88 (64-99) | 88 (64-99) | 90 | 90 (68-99) | 90 (68-99) |
| Cambio promedio en el recuento plaquetario, x109/L; Promedio (IC95% o DE) | 91c (67-116; P<0.001) | 94 (56) P=0.001 (wk 104) | 136 (41) P=0.007 (wk 156) | NR | NR | NR |
| Aumento en TFGe ≥ 15 ml/min /1.73m2; % | 53 | 59(33-82) | 59 (33-82) | 15 | 40 (19-64) | 40 (19-64) |
| Disminución en la creatinina sérica ≥25%; % (IC 95%) | 76 | 76 (50-93) | 76 (50-93) | 35 | 55 (32-77) | 55 (32-77) |
| HRQL cambio promedio en el puntaje EQ-5Db (IC 95% o DE) | 0.30 (0.25 – 0.35; P<0.001) | 0.31 (0.28-0.34; P< 0.0001) semana 104 semana 152 | 0.29 (0.28-0.330; P<0.0001) | 0.13 (0.08 – 0.18; P< 0.001) | 0.12 (0.15) semana 104 | 0.16 (0.24) semana 152 |

Abreviaturas: HRQL: Calidad de vida relacionada con la salud; NR: No reportado; a. La duración promedio del tratamiento fue 100 semanas con un rango de 2 a 186 semanas. 5 pacientes permanecieron en el estudio durante más de 130 semanas; b. Definido por las mediciones de LDH y plaquetas durante 2 mediciones ≥4 semanas de diferencia; b. (está repetida la b)Umbral clínicamente significativo ≥0.06; c. A lasemana 60.

For patients <18 years of age, manage eculizumab based on body weight according to the following recommendation (table 2)[56]

For patients <18 years of age, manage eculizumab based on body weight according to the following recommendation (table 2)[56]

## Conclusions

aHUS is considered as an ultra-orphan disease ; more than 50% of the patients die, or need renal replacement therapy or suffer from end-stage kidney failure within the first year of diagnosis. It is a chronic illness caused by alteration in the regulation of the complement system. The alternate path is always "on" and can auto amplify its activity under different conditions known as amplifiers of the snap-in (trauma, infections, among others). The conditions previously mentioned create an immediate immune and hematologic response, which leads to endothelial lesion and vascular stenosis microangiopática. Consolidating the diagnosis of TMA that leads to ischemia of multiple organs, including the kidney. The diagnosis of aHUS is clinical and it is based on the exclusion of other primary TMA and in the analysis of the conditions amplifiers or coexisting diseases, which are presented in up to 70% of cases.

With current treatment (plasmapheresis or plasma infusion) 9-15% of patients with aHUS die within 1 year after a clinical manifestation of hemolysis. Since 2011, the Eculizumab, a recombinant monoclonal antibody hybrid Ig2/IG4, totally humanized directed against the component C5 of human complement is available. Multiple studies have demonstrated its effectiveness to control, the increased activity of the complement with hematological, renal and systemic improvement, reflected in the quality of life and long-term prognosis. The severe consequences of this disease reinforce the importance of accurate diagnosis and adequate knowledge of the different TMA, since its treatment differs today, with the

blockage of C5 a core component of early treatment for aHUS.

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## Conflict of interest:

Doctors Zilac Espitaleta, Light Estela Gonzalez, Milton Ibarra, Luis Alfonso Valderrama and Juan Pablo Cordoba, have received fees for academic lectures on Atypical Hemolytic Uremic Syndrome (aHUS) by Alexion pharmaceuticals. The doctor Juan Pablo Cordoba has served as an external consultant for pharmaceutical Alexion.

| Patient weight | induction | Maintenance |
|---|---|---|
| 40 kg and more | 900 mg per week x 4 dose | 1200 mg per week 5; then 1200 mg per 2 weeks |
| 30 kg less than 40 kg | 600 mg per week x 2 dose | 900 mg per week 3; then 900 mg every 2 weeks |
| 20 kg less than 30 kg | 600 mg a la semana x 2 dosis | 600 mg per week 3, then 600 mg every 2 weeks |
| 10 kg less than 20 kg | 600 mg a la semana x 1 dosis | 300 mg per week 2; then 300 mg every 2 weeks |
| 5 kg less than 10 kg | 300 mg per week x 1 dose | 300 mg per week 2; then 300 mg every 3 weeks |

1. the use of Eculizumab as first-line therapy in patients confirmed with aHUS or recurrence of aHUS after transplant is recommended.
2. In patients where therapeutic response due to plasma exchange is not observed or a dependency on the therapy is observed; one should consider Eculizumab as therapeutic strategy in patients with TMA
3. In our opinion, given that there is a lack of studies oriented to the ideal duration of therapy must be personalized for each case and suspending treatment should because of the risk of relapse..

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