A new era in the diagnosis and treatment of atypical haemolytic uraemic syndrome

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ABSTRACT

The haemolytic uraemic syndrome (HUS) is characterised by haemolytic anaemia, thrombocytopenia and acute renal failure. The majority of cases are seen in childhood and are preceded by an infection with Shiga-like toxin producing Escherichia coli (STEC-HUS; so-called typical HUS). Non-STEC or atypical HUS (aHUS) is seen in 5 to 10% of all cases and occurs at all ages. These patients have a poorer outcome and prognosis than patients with STEC-HUS. New insights into the pathogenesis of aHUS were revealed by the identification of mutations in genes encoding proteins of the alternative pathway of the complement system in aHUS patients. Specific information of the causative mutation is important for individualised patient care with respect to choice and efficacy of therapy, the outcome of renal transplantation, and the selection of living donors. This new knowledge about the aetiology of the disease has stimulated the development of more specific treatment modalities. Until now, plasma therapy was used with limited success in aHUS, but recent clinical trials have demonstrated that patients with aHUS can be effectively treated with complement inhibitors, such as the monoclonal anti-C5 inhibitor eculizumab.

KEYWORDS

Atypical haemolytic uraemic syndrome, complement system, eculizumab, kidney transplantation, plasma therapy

INTRODUCTION

The haemolytic uraemic syndrome (HUS) is a rare and severe thrombotic microangiopathy (TMA) characterised by the triad of haemolytic anaemia, thrombocytopenia and acute renal failure. HUS is characterised histologically by vascular abnormalities with glomerular endothelial damage, swelling of the endothelium, endothelial detachment of the basement membrane, intima fibrosis, and thrombosis. In table 1, the most important causes of thrombotic microangiopathies (both HUS and thrombotic thrombocytopenic purpura [TTP]) are shown.¹,²

Table 1. Causes of haemolytic uraemic syndrome and thrombotic thrombocytopenic purpura

<table>
<thead>
<tr>
<th>Infectious</th>
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<tbody>
<tr>
<td>Infection with Shiga-like toxin producing <em>Escherichia coli</em> (STEC)</td>
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<tr>
<td>Infection with neuraminidase producing <em>Streptococcus pneumoniae</em></td>
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<td>Human immunodeficiency virus (HIV)</td>
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<th>Complement dysregulation</th>
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<tr>
<td>Genetic abnormalities in complement (regulating) proteins</td>
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<td>Acquired defects (autoantibodies against CFH)</td>
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<tr>
<th>ADAMTS13 deficiency</th>
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<tr>
<td>Genetic abnormalities</td>
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<td>Autoantibodies against ADAMTS13</td>
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<th>Clinically associated with</th>
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<tr>
<td>Systemic diseases: SLE, antiphospholipid syndrome, defective cobalamin metabolism</td>
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<tr>
<td>Medication: ticlopidin, mitomycin, bleomycin, cisplatin, quinine, tacrolimus, cyclosporin, rifampicin, clopidogrel</td>
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<tr>
<td>Malignancies: chemotherapy</td>
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<td>Viruses: cytomegalovirus, parvovirus</td>
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<td>Transplantation: calcineurin inhibitors, rejection</td>
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<tr>
<td>Pregnancy: oral contraceptives, pre-eclampsia, HELLP syndrome</td>
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<tr>
<td>Glomerulopathies: MPGN type II</td>
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<tr>
<td>Bone marrow transplantation: radiation, medication, graft vs host disease</td>
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</table>

ADAMTS13 = a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; CFH = complement factor H; HELLP = haemolysis, elevated liver enzymes and low platelets; MPGN = membranoproliferative glomerulonephritis; SLE = systemic lupus erythematosus.
In more than 90% of the cases, the disease is triggered by an infection with Shiga-like toxin producing *Escherichia coli* (STEC). Especially young children between two and six years of age are sensitive to the development of the disease. Three to eight days after contamination with the bacteria, the patient develops abdominal pain with watery and/or bloody diarrhoea, followed within 24 hours by haemolytic anaemia, thrombocytopenia, and acute renal failure. This HUS is also called typical or diarrhoea-associated HUS (D+ HUS) or STEC-HUS. Mortality in children with STEC-HUS is 3 to 5% during the acute phase of the disease; about 75% of the patients completely recover after an episode of STEC-HUS.4

While STEC-HUS is indeed mostly seen in children, in the recent world’s largest STEC outbreak in Germany, mostly adults above 20 years and predominantly females were affected. This was attributed to the changes in the microbial characteristics of the bacteria (STEC O104:H4), which shares virulence characteristics of typical STEC strains and enteraggregative *E. coli* strains,5 indicating that changes in the bacterial characteristics can lead to changes in host profile. Although a greater proportion of patients infected with STEC O104:H4 eventually developed HUS,5 both clinical course of individual patients and mortality (4%) seemed to be comparable with historic reports.5,6

Non-STEC-HUS is seen in 5 to 10% of all HUS cases, can appear at any age and may be sporadic or familial. These patients have a poor prognosis with a high mortality and morbidity in the acute phase of the disease and progression to end-stage renal disease (ESRD) in 50% of the cases.7,8 Many causes of this so-called atypical HUS (aHUS) have been identified (table 1). The recently recognised disorders of complement regulation will be outlined in this review. Other associations include various non-enteric infections (especially *Streptococcus pneumoniae* infections), viruses, malignancies, drugs, bone marrow and kidney transplantation, pregnancy, and systemic diseases.

Atypical HUS needs to be distinguished from TTP, although they overlap clinically and morphologically. Both diseases share features of a thrombotic microangiopathy, caused by activation and damage of endothelial cells. In aHUS this is mostly confined to the glomerular endothelium, while in TTP there is more systemic vascular endothelial damage. Histological studies revealed that thrombi of patients with TTP mostly contain thrombocytes, while HUS thrombi are positive for fibrin instead of platelets.9 Neurological symptoms and thrombocytopenia prevail in TTP, while kidney failure is limited. In aHUS, on the other hand, kidney failure is the most important clinical symptom. On clinical grounds it may be difficult to differentiate between aHUS and TTP and this may cause a delay in treatment. The discovery of the specific involvement of ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) in the pathogenesis of TTP has allowed discrimination between the two TMAs: in patients with TTP, ADAMTS13 activity is greatly reduced (5 to 10% of normal). This is mostly due to autoantibodies against ADAMTS13. Congenital TTP, caused by mutations in the ADAMTS13 gene, is an extremely rare autosomal recessive disease (incidence 1:1,000,000), which manifests often, but not exclusively, at birth or during childhood.10 Ten to 25% of TTP patients, however, have normal ADAMTS13 activity, suggesting the presence of as yet unknown physiopathological mechanisms.

In this review, we will further focus on the role of the complement system in the pathogenesis, outcome, and treatment of atypical HUS.

## The Complement System and Atypical HUS

Already in the 1970s decreased plasma levels of the complement proteins C3 and complement factor B (CFB) in both sporadic and familial cases of HUS were identified.11 The presence of increased breakdown products of these proteins suggested that activation of the alternative pathway of the complement system could be involved in the pathogenesis of the disease.12 In the last decade, indeed, a clear link was demonstrated between aHUS and genetic abnormalities in complement (regulating) genes, which can result in hyperactivation of the complement system, eventually leading to glomerular endothelial activation and thrombosis.

**Activation and regulation of the complement system**

The human complement system is part of the innate immunity and consists of more than 40 plasma and membrane-associated proteins. The most important roles of the complement system are the recognition of pathogens (opsonisation), the activation and chemotaxis of leucocytes, and the induction of cell lysis by incorporation of the membrane attack complex (MAC).13-15 Three activation pathways are recognised: the classical pathway, the mannose binding lectin pathway, and the alternative pathway. In aHUS, the alternative pathway is mostly affected.

To prevent continued and unopposed complement activation, and resulting cell damage, the complement system is tightly regulated. Each pathway has its own regulators (inhibitors), but some regulators work on more than one pathway (figure 1; inhibitors shown in italic).

Activating regulators include complement factor B and complement factor D.

Foreign surfaces that either lack membrane-bound regulators or cannot bind soluble regulators are attacked...
and damaged by the complement system. The key regulators of the alternative pathway are complement factor H (CFH), complement factor I (CFI), and membrane co-factor protein (MCP or CD46). These complement regulatory proteins are either constitutively present on the endothelial cell membrane or are bound by the endothelial glyocalyx. The mechanism of complement regulation at the cell surface by these regulators is schematically shown in figure 2A.

Mutations in complement genes in aHUS patients
A loss-of-function mutation in a complement-inhibiting gene or a gain-of-function mutation in a gene that encodes a complement activator will lead to an unopposed activation of the complement system, resulting in formation of the membrane attack complex on cell surfaces of especially endothelial cells in the microcirculation of the kidney. As a result, endothelial cells are damaged and leucocytes are attracted, releasing oxygen radicals and proteinases, which can further damage the endothelium. This will eventually result in increased platelet adherence and the formation of microthrombi in the kidney, thus explaining the characteristic triad of aHUS: acute renal failure, thrombocytopenia, and haemolytic anaemia.

In 1998, Warwicker et al. were the first to describe a mutation in the gene encoding CFH in familial cases of aHUS. Nowadays, a genetic aberration in one of the proteins of the alternative complement pathway can be found in at least 50% of the aHUS patients. Mutations, usually heterozygous, have been identified...
in the complement inhibitors CFH, CFI, MCP, and in only one single study in thrombomodulin (THBD), and in the activators C3 and CFB. In addition, aHUS is associated with the presence of a combination of single nucleotide polymorphisms in CFH (CFH TGTGT haplotype) or MCP (MCP GGAAC haplotype). Not unexpectedly, aHUS can also be caused by antibodies that impair the action of the complement regulatory proteins. Thus far, autoantibodies against CFH (αFH) have been identified in aHUS patients. These αFH autoantibodies can block the epitopes of CFH that are involved in binding to the endothelial cell membrane, resulting in defective regulation of the complement at the site of the endothelium, leading to endothelial damage. The development of these αFH antibodies is associated with a polymorphic homozygous deletion of complement factor H related proteins (CFHR1 and CFHR3). Mechanisms of disease for several mutations are shown in figures 2B-D.

Complement investigations in aHUS patients
Recent guidelines suggest screening for complement abnormalities in patients with aHUS. Complement activity (CH50 and AP50) and serum complement components (C3, C4, C3d, CFH, and CFI) can be measured in serum, drawn before the start of therapy. It must be realised that most assays measure the presence of the protein and not the activity. Moreover, abnormalities in complement regulation may only occur at the level of the endothelial cell surface, and not systematically. Therefore, serum levels of the above-mentioned complement components may be normal in patients with complement dysregulation and thus cannot exclude a genetic complement disorder. The expression of membrane-bound MCP on mononuclear leucocytes can be investigated by fluorescent-activated cell sorting (FACS). Mutational screening should be performed in the complement genes that have been associated with aHUS.
(CFH, CFI, MCP, C3, CFB, and THBD), irrespective of serum C3, CFH, or CFI levels. The presence of αFH can be identified in serum by enzyme-linked immunosorbent assay (ELISA). ADAMTS13 activity should be measured to exclude TTP: an activity below 5 to 10% could indicate a rare cause of aHUS, such as HIV infection, pregnancy, or cobalamin deficiency, should be considered and investigated at presentation. STEC infection has to be ruled out in aHUS patients as well, as an unusual presentation of STEC-HUS can occur. In 10% of the patients no diarrhoea occurs and STEC-HUS can occur in adults as well, as in the German outbreak. An overview of the investigations to be performed in patients with aHUS is shown in Table 2.

### Incomplete penetration of aHUS

Mutations in complement (regulating) genes can be found in healthy family members: the penetrance of disease among carriers of mutations in CFH, CFI, and MCP is approximately 50 to 60%. This indicates that the genetic aberrations are probably important for the development of aHUS, but not the sole cause. Affected patients may carry combined mutations, in more than one gene, or carry a mutation in combination with the associated CFH or MCP haplotype. Family members who only carried one mutation or no polymorphisms were not affected, but this could be due to incomplete penetrance as well. Atypical HUS may not occur until adulthood, even in patients with multiple genetic defects. This indicates that an environmental factor, such as a complement trigger, is probably needed to develop the disease. For instance, Caprioli et al. reported that in 77% of the patients with a mutation in CFH, CFI, or MCP, the clinical symptoms were preceded by flulike symptoms, gastroenteritis, or other infections.

### OUTCOME OF DISEASE

In about 60% of the patients with a mutation aHUS is diagnosed during childhood and in more than half of the cases, the disease is triggered by an infection or pregnancy. Prognosis of patients with aHUS is poor, up to 25% of patients may not survive the acute phase and up to 50% of the patients progress to ESRD. However, outcome of the disease is dependent on the underlying genetic aberrations. Eighty to 90% of the patients with an MCP mutation will develop a remission, although recurrences often occur. In contrast, 60 to 70% of the patients with a CFH, CFI, or C3 mutation will develop terminal renal failure within one year after diagnosis; in patients with αFH this amount is 30%. Not many patients with an aberration in CFB have been reported yet, but in 88% of the patients of one study, renal function was lost within one year after diagnosis. The underlying complement defect also determines whether therapy is needed and if it will be effective. For instance, in patients with an MCP mutation alone, plasma therapy is of limited added value; remission is achieved in 80 to 90% of these patients without plasma treatment. Since MCP is a membrane-bound protein, a defect MCP protein cannot therefore be substituted by plasma therapy.

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**Table 2. Overview of investigations to be performed in patients diagnosed with atypical HUS**

<table>
<thead>
<tr>
<th>Underlying cause of TMA</th>
<th>Technique</th>
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<tbody>
<tr>
<td>Disorders of complement regulation</td>
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<tr>
<td>C3 and C4 levels</td>
<td>Nephelometry (serum)*</td>
</tr>
<tr>
<td>C4d levels</td>
<td>Immuno-electrophoresis (EDTA plasma)*</td>
</tr>
<tr>
<td>CFH and CFI levels</td>
<td>Radial immunodiffusion (serum)*</td>
</tr>
<tr>
<td>Autoantibodies against CFH</td>
<td>ELISA (serum)*</td>
</tr>
<tr>
<td>Surface expression MCP</td>
<td>FACS (EDTA blood)</td>
</tr>
<tr>
<td>Mutational screening, CFH, CFI, MCP, C3, and CFB</td>
<td>Sequencing analysis (EDTA blood)</td>
</tr>
<tr>
<td>ADAMTS13 deficiency</td>
<td>FRETS vWF73 (citrate plasma)*</td>
</tr>
</tbody>
</table>

**Rare HUS causes**

- Defective cobalamin metabolism
  - Homocysteine levels: HPLC (potassium-EDTA plasma)*
  - Methylmalonic acid levels: LC-Tandem MS (potassium-EDTA plasma)*
  - Mutational screening MMACHC: Sequencing analysis (EDTA blood)
  - HIV: Serology
  - Pregnancy: Pregnancy test
  - HELLP syndrome: Liver enzymes
  - Antiphospholipid syndrome: Antiphospholipid antibody
  - Systemic lupus erythematosus: - Antinuclear antibody
  - STEC infection: Culture, PCR, serology, anti-O157 antibody
  - Streptococcus pneumoniae infection: Culture, PCR, Coombs test, peanut lectin, activity test, transferrin isoelectric focussing

*Serum and EDTA plasma samples need to be centrifuged as soon as possible after sampling (preferably within 60 minutes). For the analysis of C3d, homocysteine, and methylmalonic acid levels, (potassium) EDTA blood needs to be placed on ice immediately after sampling. ADAMTS13 = a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; CFH = complement factor H; CFI = complement factor I; EDTA = ethylenediaminetetraacetic acid; ELISA = enzyme-linked immunosorbent assay; FACS = fluorescent-activated cell sorting; FRETS vWF73 = fluorescence- quenching substrate for ADAMTS13; MCP = membrane cofactor protein; HELLP = haemolysis, elevated liver enzymes and low platelets; HIV = human immunodeficiency virus; HPLC = high-performance liquid chromatography; LC-Tandem MS = liquid chromatography–tandem mass spectrometry; MMACHC = methylmalonic aciduria and homocystinuria type C protein.

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TREATMENT OPTIONS

The overall outcome of patients with aHUS is poor. To be effective, treatment must be started urgently, preferably within 24 hours after diagnosis. At this moment it takes many weeks to several months to perform the laboratory assays and genetic studies that are needed to specify the underlying cause. Furthermore, at this moment no complement abnormalities can be found in the 40% of patients. Therefore, it is advised to start plasmapheresis, which replaces missing or deficient proteins and removes disease causing antibodies, as the first treatment option. New treatment options such as complement inhibitors are now available.

Plasma therapy

Although there is no evidence from randomised controlled trials, plasmapheresis is the first-choice therapy in patients with aHUS due to a complement dysregulation. Cohort studies have shown that the mortality rate has decreased from 50 to 25% since the introduction of plasma therapy. It is suggested to exchange 1.5 times the expected plasma volume (60 to 75 ml/kg) and replace plasma in patients who are already hypertensive and volume overloaded due to renal impairment.

In the most recent guidelines, it is recommended to start plasmapheresis within 24 hours of diagnosis. It is suggested to exchange 1.5 times the expected plasma volume (60 to 75 ml/kg) and replace plasma with fresh frozen plasma or virus-inactivated pooled plasma. There are no evidence-based treatment schedules for plasmapheresis treatment reported in the literature. Guidelines published by the European Paediatric Study Group on HUS recommend the following: plasmapheresis should be performed daily for five days, then five sessions a week for two weeks, and then three times a week for two weeks. When plasma infusion is used instead of plasmapheresis, the suggested dosage is 30 to 40 ml/kg initially and 10 to 20 ml/kg per day thereafter. The dose and frequency may be reduced to weekly or biweekly intervals if plasma therapy appears to be successful.

To monitor the response to plasma therapy, the best parameters are platelet count, and lactate dehydrogenase and haemoglobin levels in serum (haematological remission). Haptoglobin levels often remain decreased after achieving haematological remission and are therefore not used as a parameter. To determine the total treatment time, no valid parameter is available, but recommendations state that treatment should be continued for at least two days after complete remission has been achieved.

However, some aHUS patients will be plasma dependent and need chronic plasma treatment to stay in remission. Furthermore, it is known that in both adults and children intercurrent infections as well as vaccinations can trigger a relapse of aHUS, for which plasmatherapy has to start again or needs to be intensified.

For patients with an MCP mutation alone, plasma therapy has limited value in the treatment of aHUS: remission is achieved in 80 to 90% of these patients without plasma treatment. MCP is a membrane-bound protein and a defect MCP protein can therefore not be substituted by plasma therapy. However, since it is not known which complement genes are involved in the pathogenesis of aHUS at first presentation and since it is known that combined mutations in complement genes can occur, plasma therapy remains the first choice of treatment.

Besides plasmapheresis, avoiding triggers of endothelial injury, such as hypertension and hypercholesterolaemia, by adequate blood pressure control and the use of statins are important treatment options in the acute phase of the disease and should be maintained once in remission.

Transplantation

The clinical outcome of renal transplantation in patients with aHUS is dismal. Approximately 50% of patients with aHUS will develop recurrent disease and graft loss. There are no clinical predictors of outcome, although the use of a calcineurin inhibitor after transplantation is associated with an even higher recurrence rate.

Unfortunately, patients with aHUS are also more prone to develop acute rejections, which also affects graft survival. Knowledge of the underlying genetic defect is helpful in predicting prognosis. The recurrence risk in patients with a CFH mutation is 75 to 90%; for patients with a CFI mutation this is 45 to 80%, and in case of a C3 mutation, the risk of an aHUS recurrence is 40 to 70%. Recurrences have been seen in patients with CFB and thrombomodulin mutations, as well. On the other hand, patients with a mutation in the gene encoding the membrane-bound MCP have a low risk to develop a disease recurrence in the graft.

Admittedly, it can be debated whether knowledge of the underlying genetic defect affects the management of the patient with aHUS after transplantation. Patients should be informed of the high risk of recurrence, and care should be taken to minimise endothelial injury.
Therefore, it is advised to avoid long ischaemia times, not to accept kidneys of non-heart-beating donors, and not to use calcineurin inhibitors. A recurrence should be treated with plasmapheresis, and most centres would use prophylactic plasmapheresis. Indeed plasmapheresis before and after renal transplantation has been beneficial, but given the poor outcome associated with a recurrence, there is a debate on whether isolated renal transplantation should be offered to patients at high risk of a recurrence.

Some authors have suggested that a combined kidney and liver transplantation with preventive plasmapheresis should be performed in patients with a known CFH or CFI mutation. However, the risky procedure of a combined kidney and liver transplantation must be weighed against the estimated risk of recurrence. Hopefully, emerging therapies with complement inhibitors will allow successful kidney only transplantation in the near future (see below).

Knowledge of the underlying genetic defect is critical when considering a living-related kidney transplantation. Until recently, living kidney donations were considered unjustified in patients with aHUS: there is not only a high risk of graft failure in the recipient, more importantly the donor may be a carrier of the mutation and could develop aHUS due to uncontrolled complement activation during the donor procedure. If a mutation is identified in the acceptor, family members can be screened for this mutation, and only donors without this mutation can be accepted for donation. Of note, if no mutations are found, current policy is to not accept any related donor, as genetic aberrations may be present in not yet associated genes.

The burden of endothelial injury in a post-transplantation setting, caused for instance by immunosuppressive drugs, viral infections or rejection, might trigger de novo HUS in the presence of mild genetic susceptibility to HUS. Possible causes of recurrent and de novo post-transplant HUS, both genetic and environmental, are shown in figure 3. Although the influence of environmental factors leading to endothelial injury is probably higher in de novo HUS, genetic aberrations in the complement system are still found in 30% of the patients diagnosed with de novo post-transplant HUS. To minimise the environmental risks, adequate control of blood pressure and hypercholesterolaemia in combination with the prudent use of calcineurin inhibitors during renal transplantation is warranted (reviewed by Zuber et al.).

Emerging new therapies

A new drug recently registered by the FDA and EMEA for the treatment of aHUS patients is the recombinant, humanised, monoclonal anti-C5 antibody eculizumab (Soliris®, Alexion Pharmaceuticals, Cheshire, CT, USA). Eculizumab specifically binds to C5, thereby blocking the cleavage of C5 into C5a (figure 1). In this way the formation of the anaphylatoxin C5a and of the membrane attack complex C5b-9 is prevented. Eculizumab has been approved worldwide for the treatment of paroxysmal nocturnal haemoglobinuria (PNH), a haematological disease associated with loss of regulation of the terminal complement pathway on erythrocytes. Since the first successful reports of eculizumab treatment in aHUS patients, many reports have followed, describing patients who received eculizumab to rescue their native kidneys or to prevent a recurrence in a graft after transplantation (reviewed by...
Loirat et al. and Köse et al. Relapses after eculizumab treatment have only been seen when the treatment was discontinued or in patients who received a single dose; all other patients went into remission.

Two international multicentre prospective phase 2 open-label clinical trials in adolescent and adult aHUS patients and a retrospective study in children have been conducted so far. The results showed that thrombocyte levels increased and renal function already improved from the first dose of eculizumab. None of the patients required a TMA intervention (plasmapheresis or dialysis) during the treatment. Eculizumab was well tolerated in these clinical studies. Adverse effects that were most frequently reported were hypertension, upper respiratory tract infection, and diarrhoea. In STEC-HUS patients, eculizumab is not indicated as a treatment option.

As clearance of Neisseria meningitidis is highly dependent on the terminal complement pathway, patients treated with eculizumab are at a higher risk for meningococcal infection. Therefore, patients should be vaccinated at least two weeks before the start of the treatment. As vaccination does not protect against all serotypes, both patients and physicians should be aware of early signs of meningococcal infection. Attention also has to be paid to patients treated with immunosuppressive drugs, as these therapies can reduce the response upon vaccination.

Eculizumab is very expensive: current estimates are up to € 300,000 per treatment year. Although this drug certainly has changed the future perspectives of patients with aHUS, many unsolved questions remain: who should receive the drug, what treatment schedules should be used, and how long should therapy be continued. It is even undecided if prophylactic treatment is needed. Cost-effectiveness should be evaluated in carefully conducted prospective cohort studies.

**CONCLUSIONS**

The atypical haemolytic uraemic syndrome is a multigenetic and multifactorial disease associated with predisposing genetic variation in genes encoding proteins involved in regulation and activation of the alternative complement pathway. Other factors, including genetic polymorphisms, environmental factors, medication, and systemic disease, may contribute to the development of aHUS. Plasma therapy is still the first choice of treatment, but new treatment possibilities, such as the complement inhibitor eculizumab, may change this in the near future.

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