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EDITORIAL

# Kidney transplantation in atypical haemolytic uraemic syndrome (aHUS): a cheap way out?

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The C5 monoclonal antibody eculizumab is one of the newer biologicals that are the subject of many exciting discussions, not only because of their extraordinary high price, but also because of their high therapeutic potential in diseases in which uncontrolled activation of the complement system plays a central role. As a consequence, the list of difficult to treat inflammatory diseases eligible for treatment with this monoclonal antibody is steadily increasing. Examples are (catastrophic) anti-phospholipid syndrome, the HELLP syndrome, membranoproliferative glomerulonephritis type II, humoral transplant rejection and haemolytic uraemic syndrome (HUS).

HUS is a rare disease, characterised by the occurrence of haemolytic anaemia, thrombocytopenia and acute renal failure, rapidly progressing to end-stage renal disease (ESRD). Histological examination of the kidney reveals, amongst other things, activation and damage of glomerular endothelial cells and consequent thrombotic micro-angiopathy (TMA). Glomerular tufts are destroyed and kidney failure ensues.

In 90% of cases, the disease is caused by a *Shiga* toxin-producing *E. coli* infection. In the remaining cases a dysregulation of the complement system underlies the pathogenesis. Different causes have been discovered: mutations in genes encoding regulatory proteins of the alternative complement activation pathway, such as complement factor H (CFH), complement factor I (CFI), membrane cofactor protein (MCP) or mutations in genes encoding the two proteins of C3 convertase: complement factor B (CFB) or C3; polymorphism in genes involved in complement inhibition; or autoantibodies directed against CFH.[1] Several data point to a second hit: viral infections, some drugs or – in case of a transplanted patient – the occurrence of rejection may all trigger the disease.[2-4]

In general, kidney transplantation offers the best solution for patients with ESRD in terms of morbidity and mortality as compared with other forms of renal replacement therapy. However, for patients with aHUS, kidney transplantation may not be so favourable because the chance of recurrence in the graft may be as high as 80% with an equally high chance of graft loss, depending on the causative mutation.[4,5] Most recurrences occur in the first year after transplantation and are difficult to diagnose before irreversible damage to the graft has occurred, since it is not uncommon that the TMA is confined to the graft.[6-8] Risk factors for recurrence are the type of causative mutation, factors that are harmful for endothelial cells and/or triggers of complement activation which are usually present following transplantation: ischaemia-reperfusion injury, rejection, infection, hypertension and the use of certain drugs, such as calcineurin-inhibitors or mTOR-inhibitors.

Until the introduction of eculizumab, treatment of (recurrent) aHUS consisted of plasmapheresis, which offers a burden to the patient, since after the initial daily treatments, it has to be performed twice to three times a week. Thus, despite transplantation, the patient remains dependent on a haemodialysis-like treatment with all the inherent disadvantages. More importantly, this treatment has limited success, depending on the underlying abnormality. About two-thirds of patients with mutations in genes for factor H, factor I or C3 may respond to treatment with plasmapheresis. In contrast, in patients with MCP deficiency, no differences in remission rates with or without plasmapheresis were shown.[2] In that respect, eculizumab did indeed appear to be a miracle drug, being very effective and making the patient independent of the hospital.[9-12] Its mode of action relies on binding to the complement protein C5, by which cleavage into C5a and C5b is prevented. Blocking the formation of C5b inhibits the subsequent formation of terminal complex C5b-9 (membrane attack complex, MAC). By that, complement-mediated injury is very effectively inhibited. Issues as optimal dosing and length of treatment of

eculizumab are still unanswered. However, at around € 400,000 per patient per year, the drug is prohibitively expensive.

In this issue of the Netherlands Journal of Medicine, Verhave *et al.* describe a strategy to avoid the use of eculizumab following kidney transplantation in aHUS. They aimed to prevent or postpone recurrence of aHUS by a treatment protocol that minimises endothelial damage following kidney transplantation. They accepted only living donors in order to minimise cold ischaemia time and ischaemia-reperfusion injury. In addition, they used low-dose calcineurin inhibition in order to avoid additional insults to the endothelium. Finally, the authors achieved regulation of blood pressure and lipids by treatment with RAAS inhibitors and statins, which may prevent endothelial damage.[13] With a follow-up of 16-21 months, this strategy was successful in four consecutive patients, which is more than might be expected by chance.

If confirmed, these findings offer hope for a selected group of aHUS patients. The data are important because they show that the new drug eculizumab is not always necessary to prevent recurrence of aHUS following kidney transplantation, let alone that every patient would have to be treated prophylactically, as has recently been advocated.[11,14] However, it is unlikely that triggers of complement activation can be completely eliminated in all patients. Rejection occurs in 10-15% of recipients with the best available immunosuppressive drug regimens and may occur beyond the first year after transplantation.[15,16] Rejection incidence may be even higher when specific risk factors such as allo-immunisation, as may occur after pregnancy, transfusion or previous organ transplantation, are present. None of the patients in the report by Verhave *et al.* were immunised; none suffered from a rejection episode. Another known risk factor for the occurrence of aHUS is infection. In that respect, cytomegalovirus (CMV) is in a particular position: first, because it frequently reactivates under immunosuppression and second, because endothelial cells are activated and damaged by CMV infection.[17] Two of the four patients described by Verhave *et al.* were not at risk for CMV infection. Whether CMV reactivation occurred in the other two patients is not mentioned.

Currently, patients with aHUS have to be screened for abnormalities in the complement system before placing them on the waiting list for transplantation, in order to help in predicting their prognosis. When a living related donor is available, this donor should not possess a similar genetic abnormality. This is because it could trigger development of aHUS in the donor himself because of uncontrolled complement activation during the operation procedure.[18] The choice for a living donor to shorten cold ischaemia time and to minimise the risk of endothelial activation should be balanced against the high risk of allograft loss by recurrence of aHUS. Any decision in this respect should be carefully discussed with the individual recipient and the donor in question. When it is decided to wait for a postmortal donor, the use of non-heart-beating donors should be avoided because of the expected long cold ischaemia time and increased risk of ischaemia-reperfusion injury.

Regarding choice of immunosuppressive drug regimen, Verhave *et al.* propose to use calcineurin inhibitors (CNI) in such a dose that rejection episodes can be avoided on the one hand, while minimising endothelial activation on the other hand. Indeed, Artz *et al.* showed that initial use of cyclosporine as part of the immunosuppressive regimen significantly increased the risk of recurrence.[4] However, a recent study by Le Quintrec *et al.* failed to demonstrate a significant relationship between CNI therapy and recurrence of aHUS.[19] In contrast, they showed a significant association between use of mTOR inhibitors, known to induce endothelial cell activation,[20] with the risk of recurrence of aHUS. In view of the demonstrated adverse effects of CNI in some clinical studies[4,21,22] and their known detrimental effects on endothelial cells *in vitro*,[23] the policy as proposed by Verhave *et al.* to use low dosages seems meaningful.

Verhave's suggestion to set up a clinical trial studying the most optimal treatment strategy in patients with aHUS who receive a kidney transplant is to be welcomed. However, such a trial would probably require many more patients than are available, even in a multicentre design. Moreover, in order to get useful answers, the patients should be classified according to their genetic abnormality, corresponding severity of the disease and risk of recurrence. In the meantime, an endothelium-protective approach, i.e. selection of a living donor and avoidance of both triggers of complement activation and drugs potentially activating endothelial cells, is indeed worth following.

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