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C5 Inhibition in Secondary Thrombotic Microangiopathies: A Yet Unresolved Question

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Kidney Int Rep (2021) **6,** 878–880; https://doi.org/10.1016/j.ekir.2021.02.012

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C5 inhibitor, eculizumab, has revolutionized the management of the primary, complement-dependent, atypical hemolytic uremic syndrome (aHUS) by dramatically decreasing the rate of end-stage renal disease (ESRD) from approximately 50% in historical cohorts to 6% to 15% after treatment.[1] This benefit on kidney function clearly counterbalances the risk of meningococcal infection under eculizumab therapy and its huge cost.

Unlike aHUS, secondary thrombotic microangiopathies (TMAs) represent a large and heterogenous group of diseases including connective tissue disorders.

In scleroderma renal crisis (SRC) and idiopathic inflammatory myopathies (IIMs), vascular lesions are found predominantly in kidney biopsy specimens[2,3] and may trigger TMAs, which, in contrast to aHUS, may not be the consequences of complement dysregulation. However, in the absence of any other specific treatment, the use of C5 inhibitors is tempting in order to improve the patient prognosis. Potential efficacy of eculizumab in secondary TMAs has been reported by some research groups through case reports and case series.[4]

What Did This Study Show?

In this issue, the study from Gouin et al.[5] presents a real interest by describing the effects of eculizumab in a large retrospective series of 18 patients suffering from secondary TMA associated with SRC and IIM, an uncommon complication of these rare diseases.

Importantly, despite adequate treatment with converting enzyme inhibitors, renal prognosis of TMA-SRC seems to be very poor. Indeed, early need of dialysis was found in 7 of 11 patients (64%) and persisted until the end of the study. These results are consistent with the rate of dialysis requirement previously reported in the literature (52% to 100%), but many patients could also be weaned from dialysis within 6 months after SRC (23% to 29%).[2] This worse renal outcome without reversibility in the current cohort can be explained by the shorter follow-up time (median: 58 days [interquartile range 31 to 127 days]). In addition, 3 of 4 deceased patients had been given eculizumab in TMA-SRC, and no improvement in overall survival rate was observed (52%), compared to a survival rate of 64% to 81% in previous publications about SRC.[2]

Interestingly, the hematological features of TMA seemed to improve under eculizumab with a rapid increase in platelet count. However, this treatment was not associated with a better renal prognosis compared to the untreated patients in SRC, and compared to previous cohorts.[2] Furthermore, the investigators failed to show evidence of efficacy in SRC despite treatment being initiated at an early stage of the disease, with a median time (admission to treatment) of 6 days.

This cohort showed a better survival rate in the seven patients with IIM (72% compared to 19% in a historical cohort). However, the historical cohort was a publication of a case series with a review of the literature about 16 patients with TMA-IIM, 9 of them having been published in 2000 or earlier. These historical controls received less rituximab, methrotrexate or intravenous immunoglobulins than the actual series, so the impact of eculizumab, administered in all but one patient, should be interpreted cautiously. As discussed by Gouin et al.,[5] the complement system could be implicated in the pathogenesis of these diseases, as described in dermatomyositis but also in anti-synthetase syndrome.[6] By blocking the formation of C5b9, it is possible that muscle inflammation can also be reduced in cardiomyocytes.

Further investigations are necessary to evaluate the exact role of the complement in lesions induced by IIM.

Kidney histological features, obtained in 15 patients, showed patterns of glomerular TMA in half of the patients and arteriolar TMA in all but one. Interestingly, C5b9

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staining was shown in arterioles in seven of nine patients, which likely indicates an activation of the complement pathway. Whether, this activation is pathogenic and plays a role in the TMA lesions or is a secondary event with no relation with TMA remains unknown.

In summary, this publication by Gouin et al.[5] highlights a potential benefit of C5 inhibition on hematological TMA and on survival rate in TMA-IIM. It seems that there is no benefit to kidney function despite the presence of C5b9 in kidney biopsy specimens.

Complement System: Activation Differs From Dysregulation

Dysregulation of the complement system is well described in aHUS with the presence in 60% of the patients of a genetic predisposition — rare variants encoding proteins regulating the alternative pathway — or acquired antibodies against factor H.[1] In this disease, the efficacy of C5 inhibition is clear with a major improvement in renal prognosis. In secondary TMAs, implication of the complement system is less obvious, with a completely different genetic background. As shown in a recent study, the prevalence of rare variants in genes regulating the alternative pathway is similar to unaffected controls.[7]

As discussed by Duineveld and Wetzels,[8] complement activation is well-described in secondary TMAs, but activation differs from dysregulation. Whereas endothelial lesions in aHUS are the consequence of dysregulation of the complement system, specifically the alternate pathway at the endothelial cell surface,[1] in IIM and SRC the complement system is probably secondarily activated, possibly through the classical pathway in fluid phase, and C5 inhibition fails to solve the initial cause. This is also the case for typical HUS, which is caused by infection with bacteria producing shiga toxins. These shiga toxins lead to endothelial lesions and secondary activation of the complement system in a limited way. In this setting, C5 inhibition failed to show any benefits in retrospective studies with large population (outbreak of typical HUS occurring in Germany, 2011) including a well-designed case control study.[8]

A Need for Randomized Control Trials

The question about the efficacy of C5 inhibition in secondary TMAs will not be answered until well-designed prospective randomized controlled trials are performed, even if such trials will be difficult to complete due to the low number of cases. At the present time, short, uncontrolled, retrospective case series may provide encouraging results but not definitive proof. In addition, the absence of preselection of patients susceptible to respond to C5 inhibition could lead to negative studies. Some research teams developed an *ex vivo* test evaluating potential dysregulation of complement pathway, first shown in aHUS, then studied in some secondary TMAs such as malignant hypertension.[9] This test involves incubating immortalized human dermal microvascular endothelial cells (HMEC-1) with the patient's serum *ex vivo* and quantifying C5b9 deposits through immunofluorescence. In malignant hypertension, patients with massive *ex vivo* C5b9 formation on the endothelium showed more prevalent pathogenic variants in complement genes and may benefit from eculizumab treatment.[9] More in-depth characterization must be performed in secondary TMAs as it could allow us to identify patients likely to be susceptible to the potential efficacy of C5 inhibition.

In conclusion, this study provides further knowledge regarding the use of C5 inhibitors in the field of secondary TMAs. However, the evidence seems insufficient to consistently implement this treatment considering its potential side effects, its cost, and the lack of definitive proof of its efficacy. Randomized control trials are required to solve this challenging question.

DISCLOSURES

AW has nothing to declare. ER declares grants, and fees from Alexion Pharmaceuticals.

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