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Exceptional Case

EXCEPTIONAL CASE

Aliskiren as an adjunct therapy for atypical hemolytic uremic syndrome

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ABSTRACT

Direct renin inhibitors (DRIs) block the activation of the alternative complement pathway *in vitro* and could be a treatment option for refractory hypertension in atypical hemolytic uremic syndrome (aHUS). A 20-year-old male presented with primary aHUS complicated by end-stage renal disease and refractory malignant hypertension despite being on five antihypertensive medications at maximum dose. Only a partial response was achieved with aliskiren and eculizumab, but after increasing aliskiren to a supratherapeutic dose, antihypertensive medication was reduced, platelets increased, C3 increased and epoetin alfa requirement decreased. DRI may be an adjunct treatment for malignant hypertension associated with aHUS.

Keywords: alternative complement pathway, atypical hemolytic uremic syndrome, direct renin inhibitors, malignant hypertension

BACKGROUND

Atypical hemolytic uremic syndrome (aHUS) is associated with dysregulation of the alternative complement pathway, microvascular thrombosis and multiple organ dysfunction [1]. Recent studies suggest that renin inhibition may also regulate the alternative complement pathway by blocking the cleavage of complement component 3 (C3) upstream to the action of eculizumab [2]. We present a case of primary aHUS that derived additional therapeutic benefit from the addition of supratherapeutic aliskiren to eculizumab treatment.

CASE REPORT

An otherwise healthy 21-year-old male active duty US Army soldier with no history of hypertension or renal disease was transferred from an outside hospital with acute kidney injury requiring renal replacement therapy and refractory malignant hypertension with a blood pressure (BP) of 250/140 mmHg despite being on five antihypertensive medications at maximum doses, including telmisartan 80 mg daily. Labs were significant for anemia and thrombocytopenia, low haptoglobin and elevated lactate dehydrogenase. There were no significant schistocytes on the blood smear. Urinalysis was bland after his bp was controlled. Stool analysis was negative for *Escherichia coli* and Shiga toxin, and a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13) was normal. C3 was low at 64 mg/mL and renin elevated at 124 ng/mL/h (normal 0.167–5.380). An extensive secondary hypertension workup was negative for pheochromocytoma, primary hyperaldosteronism, reninoma, renal artery stenosis, aortic coarctation, hyper-/hypothyroidism, illicit drug use and autoimmune disease. Serologic workup for glomerular or autoimmune disease was negative. A renal biopsy demonstrated evidence of thrombotic microangiopathy characterized by 'bloodless glomeruli' with closed capillary loops, shriveled basement membrane and focal fibrin thrombi with segmental mesangiolysis. With the addition of aliskiren, his BP significantly improved to 160/90 mmHg even after weaning off of intravenous antihypertensive medication. The diagnosis of aHUS was made and eculizumab was initiated.

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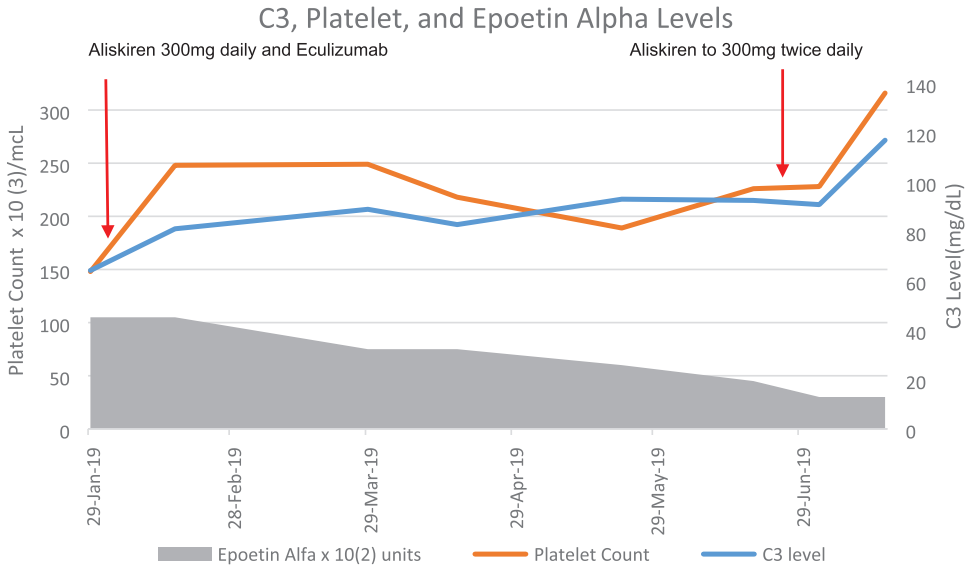

FIGURE 1: C3 level (right axis), platelet count (left axis) and epoetin alfa weekly dose (left axis units × 10^2) after initiation of eculizumab and aliskiren with a subsequent increase in aliskiren (labeled by red arrows).

After 5 months of eculizumab therapy while awaiting transplant, he clinically improved with BPs in the 100–120/70 mmHg. His C3 level improved from 60 to the 80s mg/mL (Figure 1). His hemoglobin rose from 7.5 to 11.5 g/dL with a reduction in epoetin alfa dose from 5000 to 2000 U with each dialysis treatment. His renin level declined from 124 to 10 ng/mL/h. Unfortunately, he did not recover any renal function. Since he remained on five maximum-dose antihypertensive medications and his C3 level remained low, aliskiren was increased to 300 mg twice daily. With this change he was able to transition to four antihypertensive medications at reduced doses. C3 then increased from 80 to 110 mg/mL. His platelets increased from 173 to 316 × 10^3/μL (Figure 1). His epoetin alfa dose was titrated down to 1000 U thrice weekly. In addition, the patient independently reported improved energy, activity level, appetite and sleep, with an improvement in his serum albumin from 3.8 to 5.4 g/dL. Specialty labs for aHUS revealed no identifiable genetic abnormalities or inhibitory antibodies of the alternative complement pathway. The patient remained stable for 4 months on eculizumab and supratherapeutic aliskiren without recovery of renal function before a successful kidney transplant. He remains on eculizumab and aliskiren after transplant with no evidence of recurrent aHUS.

DISCUSSION

We present a case of aHUS with malignant hypertension and end-stage renal disease. This is the first case report to our knowledge that demonstrates clinical benefit from supratherapeutic direct renin inhibition for malignant hypertension associated with aHUS. The addition of aliskiren triggered a substantial improvement in BP even while the patient was on a maximum dose of angiotensin blocker and eculizumab. In addition, doubling the dose of aliskiren allowed for a further reduction in both the number and dosages of antihypertensive medications, as well as a significant improvement in C3 and platelet levels and epoetin alfa requirements. While we cannot completely rule out a spontaneous remission or a delayed response to eculizumab, this profound clinical response was temporally associated with aliskiren initiation and subsequent dose increase. This is consistent with a recent study that showed that renin independently activates the alternative complement pathway, similar to C3 convertase, and that a renin inhibitor blocks this activation *in vitro*. Three cases of dense deposit disease in this study had a significant clinical improvement when taking aliskiren [2]. We also found that higher doses of aliskiren provided a benefit in our patient. Oh *et al.* [3] found that 600 mg provided virtually the same antihypertensive effect with no significant difference in serious adverse events in a dose range study of aliskiren 150, 300 and 600 mg/day in patients with mild–moderate hypertension but did not include malignant hypertension in their study. It is logical that higher doses may be required to combat renin levels 10–20 times normal, especially because aliskiren has low bioavailability, estimated at 2.5% [4]. Interestingly, the unexpected significant drop in serum renin levels after the initiation of a renin inhibitor suggests potential improvement of the underlying microangiopathy driving renin production. Imarikiren would be a compelling alternative treatment given it has higher bioavailability, but it is currently undergoing clinical trials and not yet widely available in the USA [5]. Our case report supports the use of a renin inhibitor for aHUS with malignant hypertension using higher doses of aliskiren until there are alternative options with higher bioavailability.

CONFLICT OF INTEREST STATEMENT

None declared. The results presented in this article have not been published previously in whole or part. The views expressed in this manuscript are those of the authors and do not reflect the official policy of the Department of the Army, Department of Defense, or the U.S. government.

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