Tailored Use of Avacopan in a Case With Refractory Antineutrophil Cytoplasmic Antibody-Associated Renal Vasculitis and Concominant Complement System Activation

To the Editor: We read with great interest the recent study by van Leeuwen *et al.*[1] regarding the compassionate use of avacopan in difficult-to-treat antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis. Avacopan is a novel promising treatment for antibody-associated vasculitis targeting the complement system by blocking C5a receptors.[2,3] Here, we report the tailored use of avacopan in a case with refractory antibody-associated vasculitis and concominant complement system activation.

An 84-year-old man with pre-existing hypertension and diabetes presented to our tertiary hospital with lower extremity purpuric papules, acute kidney injury (serum creatinine of 1.69 mg/dl, reference range: 0.5–1 mg/dl; eGFR 40 ml/min per 1.73 m^2, reference: >60 ml/min per 1.73 m^2), albuminuria (5044 mg/g creatinine, reference: <30 mg/g), and hematuria (Figure 1a–c). A skin biopsy showed dermal vasculitis, and laboratory testing confirmed presence of myeloperoxidase-ANCAs (8.4 IU/ml, reference: <3.5 IU/ml). A kidney biopsy confirmed focal class necrotizing and crescentic ANCA-associated renal vasculitis (Figure 1d). On the basis of these findings, steroid pulse (500 mg i.v. methylprednisone) and rituximab (375 mg/m^2, 750 mg) treatment was initiated for remission induction therapy. After a total number of 3 infusions of rituximab, laboratory testing showed depleted peripheral CD19+ B cells (2/µl, reference range: 100−500/µl) and regression of myeloperoxidase-ANCAs (2.2 IU/ml, reference: <3.5 IU/ml). However, kidney function and albuminuria worsened with requirement kidney replacement therapy (Figure 1a–c). A second kidney biopsy confirmed persistence of active ANCA-associated renal vasculitis (Figure 1e). On the basis of complement system activation with serum C3c lowering (0.62 g/l, reference range: 0.82−1.93 g/l) and progressive intrarenal complement C3 deposits that were not present at first presentation (Figure 1f and g), a tailored treatment with avacopan (30 mg twice daily) was initiated. Thereafter, kidney function and albuminuria improved and kidney replacement therapy was no longer required after 10 days of avacopan treatment (Figure 1a–c).

Here, we report real-life practice data on the tailored use of avacopan in a case of refractory antibody-associated vasculitis. In this case, avacopan had additional effects with respect to improved disease control and in line with previous reports.[1] Moreover, we provide the first evidence, to the best of our knowledge, that assessment of complement system activation might enable identification of patients that benefit from a complement-targeted therapy.

1. van Leeuwen JR, Bredewold OW, van Dam LS, et al. Compassionate use of avacopan in difficult-to-treat antineutrophil cytoplasmic antibody-associated vasculitis. *Kidney Int Rep*. 2022;7:624–628. https://doi.org/10.1016/j.ekir.2021.11.036

2. Jayne DRW, Bruchfeld AN, Harper L, et al. Randomized trial of C5a receptor inhibitor avacopan in ANCA-associated vasculitis. *J Am Soc Nephrol*. 2017;28:2756–2767. https://doi.org/10.1681/ASN.2016111179

3. Jayne DRW, Merkel PA, Schall TJ, Bekker P, ADVOCATE Study Group. Avacopan for the treatment of ANCA-associated vasculitis. *N Engl J Med*. 2021;384:599–609. https://doi.org/10.1056/NEJMoa2023386

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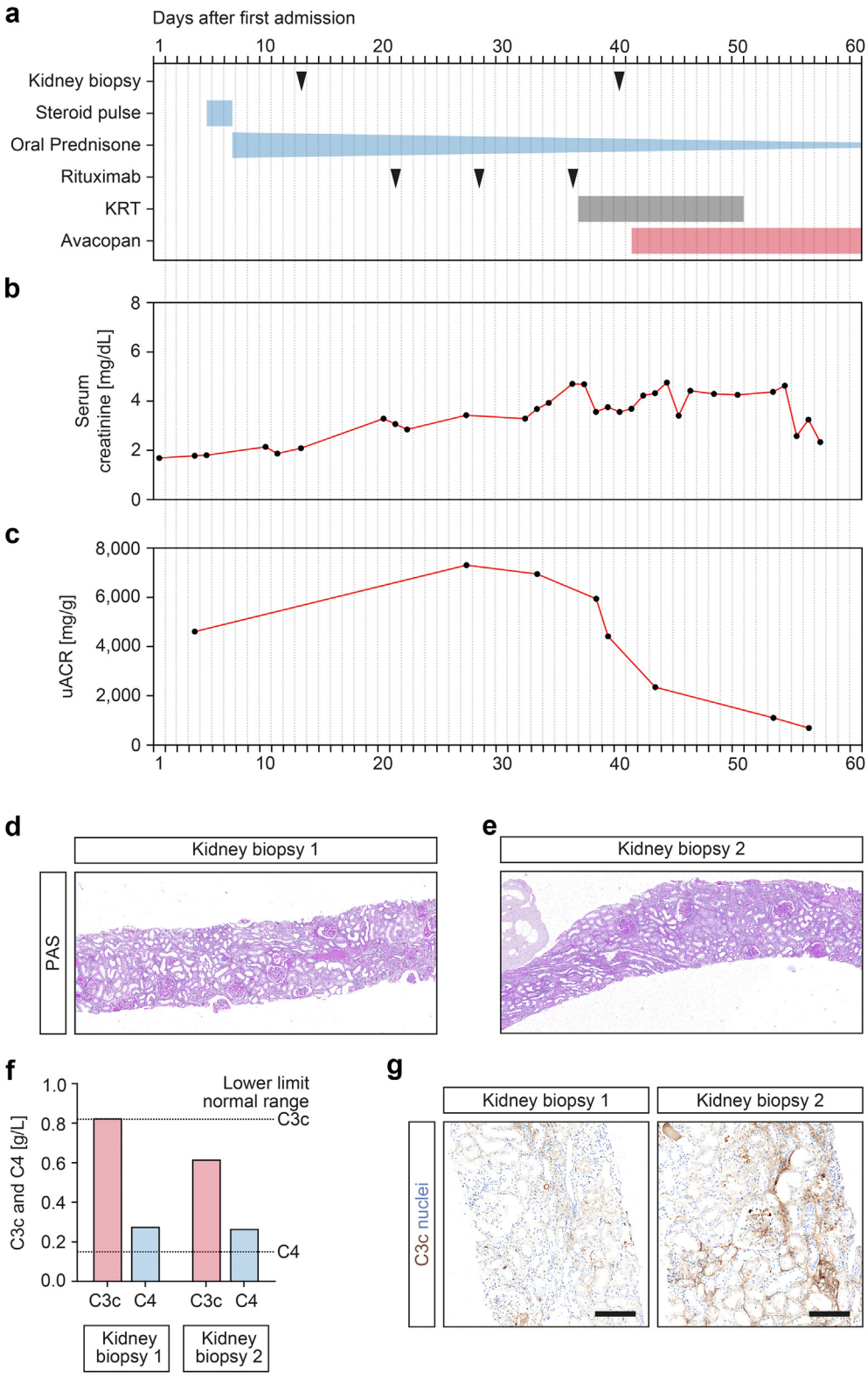

Figure 1. Avacopan improves treatment response in refractory ANCA-associated renal vasculitis with concominant complement system activation. (a) Time of kidney biopsies and treatment regimens. (b,c) Time course of serum creatinine and uACR levels. (d,e) Representative sections from the first and second kidney biopsy stained with periodic acid-schiff confirmed focal class necrotizing and crescentic ANCA-associated renal vasculitis. (f) Measurements of serum C3c and C4 at time of first and second kidney biopsy, the dotted lines represent the lower limit of the normal range. (g) Representative sections from the first and second kidney biopsy stained for intrarenal complement C3c confirmed progressive deposits (scale bar: 200 μm). ANCA, antineutrophil cytoplasmic antibody; KRT, kidney replacement therapy; PAS, periodic acid-schiff; uACR, Urine albumin to creatinine ratio.

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Response to "Tailored Use of Avacopan in a Case With Refractory Antineutrophil Cytoplasmic Autoantibody-Associated Renal Vasculitis and Concominant Complement System Activation"

The Author Replies: We appreciate the interest from Hakroush and Tampe in our manuscript describing compassionate use of avacopan in 8 difficult-to-treat patients with antineutrophil cytoplasmic autoantibody-associated vasculitis (AAV).[1] In their letter, the authors present a very interesting case of avacopan treatment in a refractory AAV patient with renal involvement.

The disease course of the patient described by the authors is in line with the disease course of 6 refractory AAV patients we previously described.[1] All patients had ongoing vasculitis activity after remission with conventional induction treatments, but reached remission shortly after the start of avacopan. The presented case, however, is unique in its observation that dialysis-dependency resolved quickly after initiating avacopan. This case emphasizes the value of real-world data, which suggest avacopan might be beneficial for patients with refractory disease.

In the era of big data analyses, it is important to appreciate that case-reports and case-series remain pivotal as hypothesis-generating clinical observations. In contrast to the pivotal randomized ADVOCATE trial that produced evidence for a steroid-free treatment strategy for active AAV patients,[2] the indication for avacopan in refractory patients is not yet clear. In addition to the unfamiliarity of physicians with this new drugs and the accompanying high drug costs of avacopan, guideline recommendations are still unclear on the place of avacopan in the treatment strategies for AAV. In the present setting, it is important to identify those AAV patients who would benefit the most from avacopan and it emphasizes the lack of an adequate biomarker predicting response or long-term remission for the use of avacopan. The authors postulate that local complement activation at the kidney tissue level might be such a potential biomarker but this requires formal validation in a larger setting. Previous studies have corroborated that low C3 serum levels are associated with worse outcomes in patient with renal involvement and are a predictor of treatment resistance in pauci-immune glomerulonephritis,[3,4] although most often, serum complement levels in AAV patients are normal.[4]

In summary, the unique and beneficial clinical observation described in the case by Hakroush and Tampe should prompt clinicians to collaborate in collecting and describing the real-world experience of treating in a low-prevalent AAV patients with a novel complement-targeting drug avacopan.

1. van Leeuwen JR, Bredewold OW, van Dam LS, et al. Compassionate use of avacopan in difficult-to-treat antineutrophil cytoplasmic antibody-associated vasculitis. *Kidney Int Rep*. 2022;7:624–628. https://doi.org/10.1016/j.ekir.2021.11.036
2. Jayne DRW, Merkel PA, Schall TJ, Bekker P, ADVOCATE Study Group. Avacopan for the treatment of ANCA-associated vasculitis. *N Engl J Med*. 2021;384:599–609. https://doi.org/10.1056/NEJMoa2023386
3. Lionaki S, Marinaki S, Liapis G, et al. Hypocomplementemia at diagnosis of pauci-immune glomerulonephritis is associated with advanced histopathological activity index and high probability of treatment resistance. *Kidney Int Rep*. 2021;6:2425–2435. https://doi.org/10.1016/j.ekir.2021.05.043
4. Augusto JF, Langs V, Demiselle J, et al. Low serum complement C3 levels at diagnosis of renal ANCA-associated vasculitis is associated with poor prognosis. *PLoS One*. 2016;11:e0158871. https://doi.org/10.1371/journal.pone.0158871

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