Low Complement C3 Levels at Diagnosis of ANCA-Associated Glomerulonephritis, a Specific Subset of Patients to Target With Anti-C5aR Therapy? In response to: Hypocomplementemia at Diagnosis of Pauci-immune Glomerulonephritis Is Associated with Advanced Histopathological Activity Index and High Probability of Treatment Resistance (Lionaki *et al.*, *Kidney International Reports*, June 2021, DOI: 10.1016/j.ekir.2021.05.043)

To the Editor: Avacopan, an anti-C5aR, recently showed comparable efficacy to corticosteroid therapy in antineutrophil cytoplasmic antibodies-associated vasculitis (AAV). Patients who would benefit most from this treatment are not yet well defined. Thus, complement-based prognostic biomarkers could be used for guiding therapy and improving outcomes. We therefore read with much interest the study by Lionaki *et al.*[1] regarding the value of low serum C3 as an independent predictor of poor prognosis in patients with pauci-immune glomerulonephritis (ANCA-GN). We aimed to compare these results with our own cohort of patients with AAV with ANCA-GN from the French Maine-Anjou registry (described elsewhere[2]) and to update our previous results on this subject.[3]

Among the 180 patients within the registry, 120 patients had serum C3 complement assessment at diagnosis. Patients who will experience end-stage kidney disease (ESKD) or death during follow-up had lower C3 levels (Figure 1a, $P < 0.05$). Only 5 patients had C3 levels below the normal range (<0.8 g/l). Thus, as previously,[3] we defined the lower C3 subgroup according to C3 median level (1.21 g/l) (Figure 1b). Patients with lower C3 levels were older (69 vs 72 years, $P = 0.04$), had worse renal function (glomerular filtration rate [GFR] 14 vs 18 ml/min, $P = 0.018$), higher proteinuria (2.7 vs 1.4 g/d, $P = 0.004$), and more frequently had MPO-ANCA (78% vs 47%, $P < 0.001$). They had more crescentic class histopathology (62% vs 33%, $P = 0.01$) and a nonsignificant increase in C3 deposition in indirect immunofluorescence (1+ vs 0+, $P = 0.12$; 58% vs 45% were classified as ≥1+, $P = 0.23$). During follow-up, they were more likely to require early (90 days from diagnosis) kidney replacement therapy (38% vs 22%, $P = 0.05$), or reach ESKD (37% vs 17%, $P = 0.015$) or death (28% vs 10%, $P = 0.012$). Survival free of ESKD or death was also lower in patients with lower C3 levels (Figure 1c, $P < 0.05$). Last, in Cox multivariable analysis, after adjustment on age and initial GFR, lower C3 level was an independent risk factor of ESKD (hazard ratio 2.17, $P = 0.043$).

In conclusion, our results are in line with and add to those of Lionaki *et al.*,[1] and confirm our previously published data.[3] Patients with a trend to low C3 levels, without hypocomplementemia *per se*, present with more crescentic lesions, more C3 deposition on kidney histopathology, and have worse renal prognosis. These data suggest a higher intra kidney complement activation[4] and a specific pathophysiology in these patients. Hence, blocking the complement alternative pathway activation through C5a receptor with avacopan may have greater effect in these patients. Prospective trials are needed to address this issue.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary References.

1. 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*. Published online June 2021:S2468024921012262. https://doi.org/10.1016/j.ekir.2021.05.043.

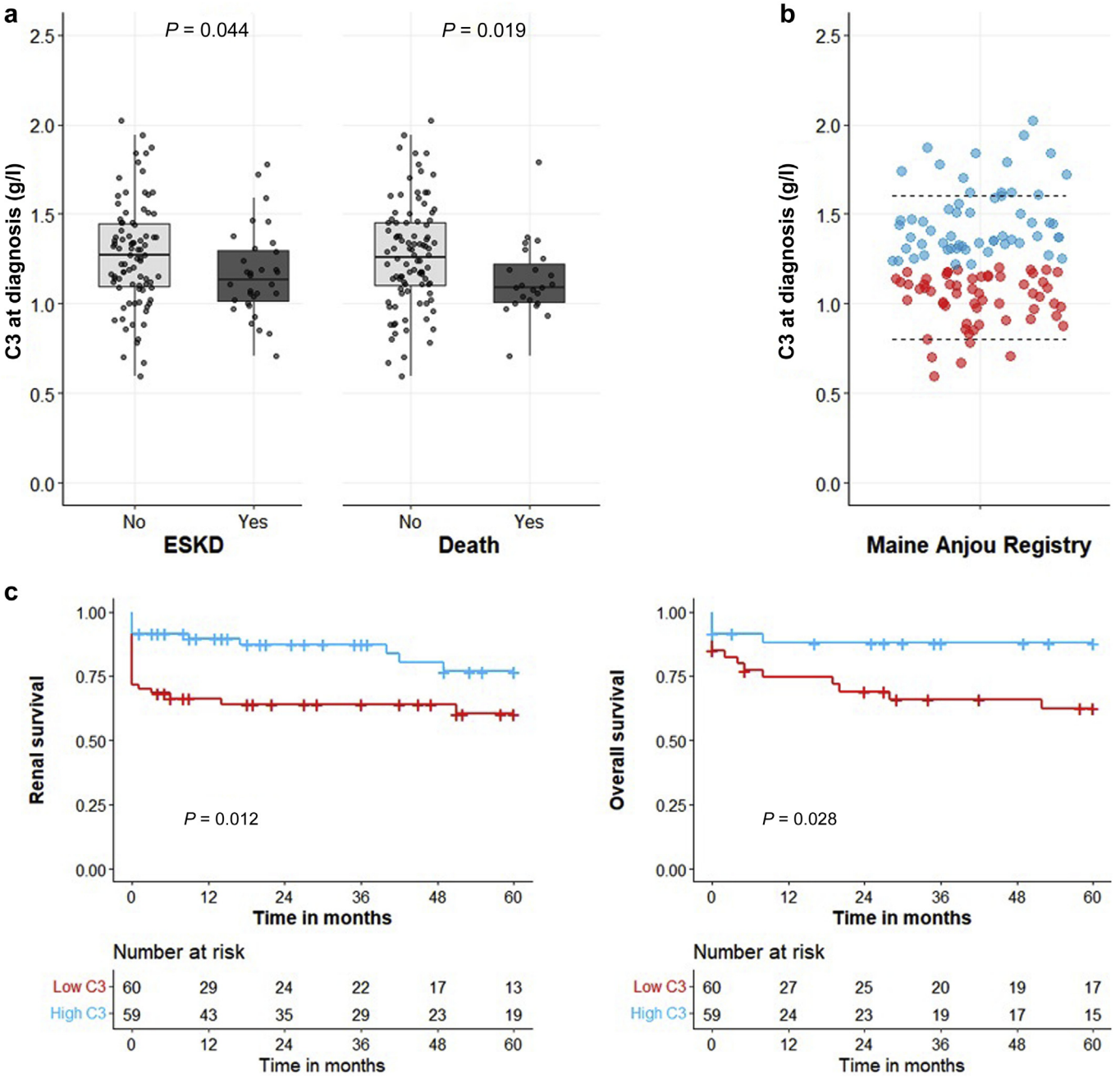

Figure 1. (a) C3 complement levels according to the occurrence of end-stage kidney disease (ESKD) or death during follow-up (boxplots show median [IQR] compared by Mann-Whitney test). (b) C3 complement levels in the cohort. Dotted lines represent upper and lower ranges of our laboratory. Low C3 subgroup is depicted in red and defined by C3 levels below median level. High C3 subgroup is depicted in blue and defined by C3 levels above median level. (c) Renal and overall survival according to low or high C3 subgroup (Kaplan-Meier curves compared with log rank test).

2. Wacrenier S, Riou J, Jourdain P, et al. Lymphopenia at diagnosis of ANCA-vasculitis with renal involvement is correlated with severity and renal prognosis. *Nephrol Dial Transplant*. 2021. forthcoming.

3. Augusto J-F, 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(7): e0158871. https://doi.org/10.1371/journal.pone.0158871.

4. Brilland B, Garnier A-S, Chevailler A, Jeannin P, Subra J-F, Augusto J-F. Complement alternative pathway in ANCA-associated vasculitis: two decades from bench to bedside. *Autoimmun Rev*. 2020;19(1):102424. https://doi.org/10.1016/j.autrev.2019.102424.

Benoit Brilland[1,2], Samuel Wacrenier[1,3], Nicolas Henry[1,4], Fanny Guibert[1,5], Giorgina Barbara Piccoli[3] and Jean-François Augusto[1,2]

[1]Service de Néphrologie-Dialyse-Transplantation, Université d'Angers, CHU Angers, Angers, France; [2]University Angers, CHU

Angers, INSERM, CRCINA, Angers, France; [3]Service de Néphrologie, Centre Hospitalier du Mans, Le Mans, France; [4]Service de Néphrologie, Centre Hospitalier de Laval, Laval, France; and [5]Service de Néphrologie, Centre Hospitalier de Cholet, Cholet, France

Correspondence: Pr Jean-François Augusto, Service de Néphrologie-Dialyse-Transplantation, CHU Angers, 4 rue Larrey, 49033 Angers CEDEX 09, France. E-mail: jfaugusto@chu-angers.fr

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