Effects of Clazakizumab on Anemia and Iron Metabolism in Patients with Kidney Failure

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JASN 00: 1–3, 2025. doi: https://doi.org/10.1681/ASN.0000000654

Clazakizumab is a high-affinity humanized mAb that targets the IL-6 ligand and inhibits downstream IL-6 function. We recently reported an approximately 90% placebo-adjusted reduction in high-sensitivity C-reactive protein (hs-CRP) in patients receiving hemodialysis with a history of cardiovascular disease and/or diabetes treated with clazakizumab.[1] In patients with kidney failure, inflammation is a key contributor to anemia and erythropoietin resistance. Through reducing inflammation, it is plausible that clazakizumab might have clinically relevant effects on anemia and iron parameters in patients with dialysis-dependent kidney failure. We therefore conducted a secondary analysis of the phase 2b randomized, double-blind, placebo-controlled POSIBIL$_6$ESKD trial to evaluate the effects of clazakizumab on anemia and iron parameters in patients receiving hemodialysis.

The phase 2b component of the POSIBIL$_6$ESKD phase 2b/3 trial evaluated the effects of clazakizumab (2.5, 5, 10 mg) or matching placebo administered intravenously every 4 weeks on a primary efficacy end point of placebo-adjusted change in hs-CRP at 12 weeks. Patients were eligible if they were receiving dialysis and had cardiovascular disease and/or diabetes and a hs-CRP >2 mg/L. Patients with chronic infections (*e.g.*, HIV, hepatitis B or C, tuberculosis), neutropenia, and chronic use of immunosuppressive agents were excluded. Ethics committees approved the trial protocol at all study sites, and all participants provided written informed consent. Detailed methods and results have previously been published.[1]

We prespecified as secondary outcomes the effects of clazakizumab on hemoglobin, iron parameters, and hepcidin. Changes in these biomarkers were assessed using mixed-effects models for repeated measures with unstructured covariance matrix, with terms for treatment, baseline, stratification level for hs-CRP, visit, and interactions between visit and each of the other model terms. We analyzed changes in key iron parameters from baseline to week 12 on the log scale as geometric mean ratios to baseline, expressed as a percentage. *Post hoc*, we reported the number and proportion of participants in each treatment arm who initiated or had their erythropoietin-stimulating agent (ESA) dose increased at week 12 compared with baseline in the safety analysis set. We performed all analyses using SAS version 9.4.

Among 127 participants, mean age and SD was 62±13 years and 42 (33%) were women. Mean (SD) hemoglobin was 10.7±1.3 g/dl, and mean (SD) transferrin saturation was 32%±12%. Median ferritin and hepcidin were 1268 (25th–75th centile 736–1598) μg/L and 232 (150–306) ng/ml, respectively. Ninety-one participants (71.7%) were receiving ESAs and 76 (59.8%) were receiving parenteral iron at baseline.

There was no effect with clazakizumab on hemoglobin at 12 weeks (Figure 1), although change in ESA dose was not restricted by protocol; mean changes in hemoglobin were +0.6±1.5, +1.0±1.3, and +1.0±1.4 g/dl in the 2.5, 5, and 10 mg clazakizumab groups, respectively, compared with +0.4±1.3 g/dl with placebo. Eighty-nine participants (70.1%) were receiving parenteral iron by the end of study,

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Published Online Ahead of Print: February 5, 2025

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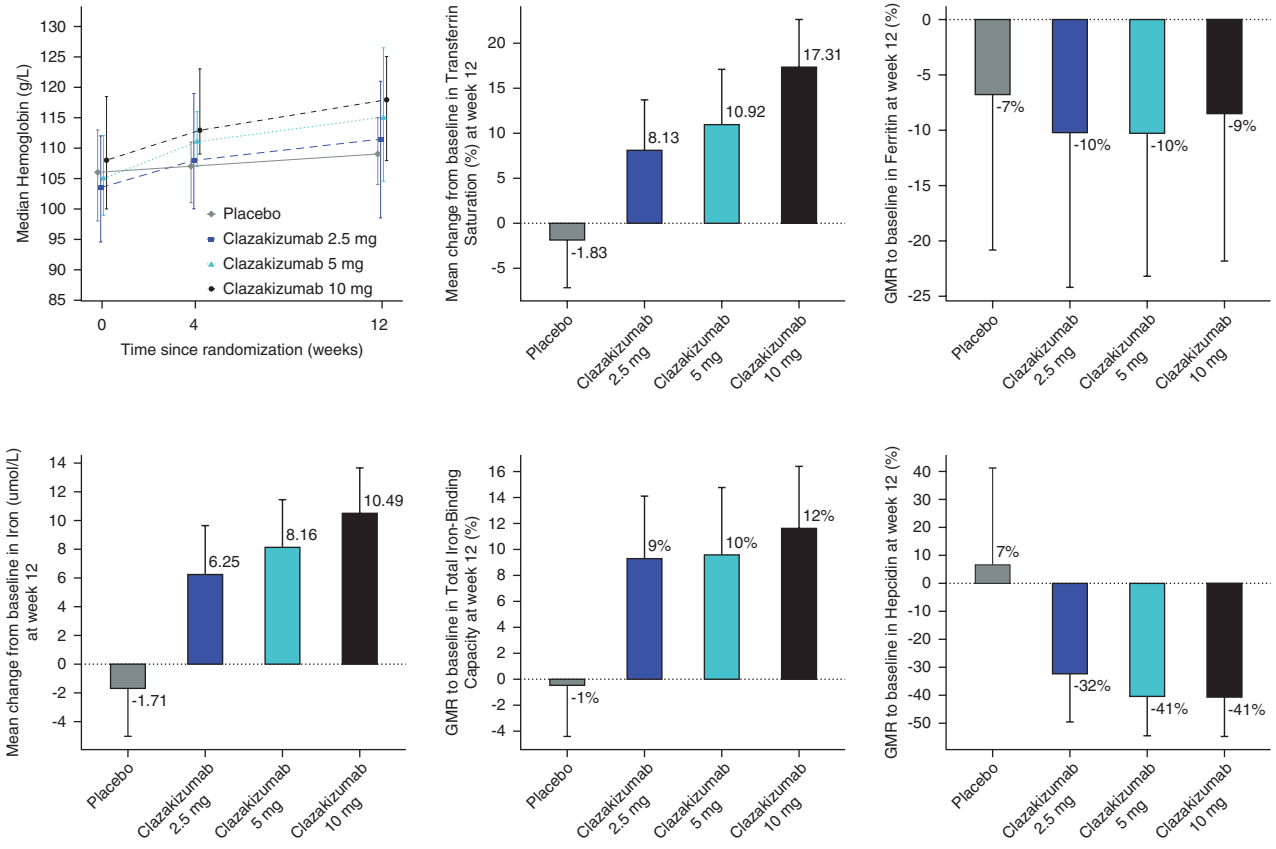

Figure 1. Effects of clazakizumab relative to placebo on change from baseline to week 12 in hemoglobin, transferrin saturation, ferritin, serum iron, total iron-binding capacity, and hepcidin. Changes from baseline to week 12 for ferritin, total iron-binding capacity, and hepcidin analyzed on the log scale as GMRs to baseline and expressed as a percentage. GMR, geometric mean ratio.

an increase that was observed across all treatment arms. Fewer participants initiated or had their ESA dose uptitrated at week 12 across higher doses of clazakizumab. In the placebo arm, eight of 30 (27%) initiated or uptitrated their ESA dose, compared with six of 30 (20%), five of 29 (17%), and two of 32 (6%) in the 2.5, 5, and 10 mg clazakizumab groups, respectively. Relative to placebo, clazakizumab increased transferrin saturation in absolute terms by 10% (95% confidence interval, 2% to 18%), 13% (5% to 21%), and 19% (12% to 27%) with 2.5, 5, and 10 mg doses, respectively. Serum iron and total iron-binding capacity were also significantly higher across all studied doses compared with placebo (Figure 1). No effect on serum ferritin was observed (Figure 1). Clazakizumab reduced serum hepcidin by −36.6% (95% confidence interval, −57.6% to −5.4%), −44.2% (−62.1% to −17.9%), and −44.2% (−62.0% to −18.2%) compared with placebo in the corresponding dose groups.

These findings build upon prior studies suggesting that IL-6 inhibition favorably affects hemoglobin and iron metabolism in patients with CKD. In a phase 1/2 placebo-controlled trial, ziltivekimab, another IL-6 inhibitor, improved iron parameters and reduced ESA dosing over 12 weeks in 61 patients on dialysis with a genetic susceptibility to IL-6–mediated inflammation.[2] In the Trial to Evaluate Reduction in Inflammation in Patients With Advanced Chronic Renal Disease Utilizing Antibody Mediated IL-6 Inhibition, ziltivekimab increased hemoglobin and improved markers of iron metabolism in 264 patients with stages 3–5 CKD.[3]

The randomized, double-blind, placebo-controlled design is a key strength of the study; however, there are some limitations. Because hemoglobin concentrations are influenced by changes in ESA dosage, changes in ESA usage may have attenuated the observed effects of clazakizumab on hemoglobin. Most of the participants were men, and median ferritin levels were relatively high, which might reduce the generalizability of these findings. The relatively short duration of follow-up did not allow for definitive assessment of the effects of clazakizumab on longer-term ESA usage. Finally, this phase of the trial only studied patients receiving hemodialysis.

More definitive data on the effects of clazakizumab on anemia, iron parameters, and ESA usage are forthcoming. The phase 3 component of POSIBIL$_6$ESKD is evaluating the effect of clazakizumab 5 mg versus matching placebo on a primary outcome of cardiovascular death or nonfatal myocardial infarction (estimated enrollment approximately 2200).

In summary, through anti–IL-6 effects, clazakizumab may improve iron utilization and reduce ESA usage in patients receiving hemodialysis.

Disclosures

Disclosure forms, as provided by each author, are available with the online version of the article at http://links.lww.com/JSN/F67.

Funding

This work was supported by CSL Behring.

Acknowledgments

Brendon L. Neuen's participation as a member of the steering committee for the POSIBIL$_6$ESKD is supported by a CVCT (CardioVascular Clinical Trials) Forum Future Trialists Fellowship. The POSIBIL$_6$ESKD trial is sponsored by CSL Behring.

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Data Sharing Statement

Data cannot be shared. The POSIBIL$_6$ESKD Trial is an ongoing combined phase 2B/3 trial program. Data sharing policies will be made available at the completion of the phase 3 component of the trial.

References

1. Chertow GM, Chang AM, Felker GM, et al. IL-6 inhibition with clazakizumab in patients receiving maintenance dialysis: a randomized phase 2b trial. *Nat Med.* 2024;30(8):2328–2336. doi:10.1038/s41591-024-03043-1
2. Pergola PE, Devalaraja M, Fishbane S, et al. Ziltivekimab for treatment of anemia of inflammation in patients on hemodialysis: results from a phase 1/2 multicenter, randomized, double-blind, placebo-controlled trial. *J Am Soc Nephrol.* 2021;32(1):211–222. doi:10.1681/ASN.2020050595
3. Pergola PE, Davidson M, Jensen C, et al. Effect of ziltivekimab on determinants of hemoglobin in patients with CKD stage 3–5: an analysis of a randomized trial (RESCUE). *J Am Soc Nephrol.* 2024;35(1):74–84. doi:10.1681/ASN.0000000000000245