Ravulizumab for the Treatment of aHUS in Adults: Improving Quality of Life

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Kidney Int Rep (2021) 6, 1489–1491; https://doi.org/10.1016/j.ekir.2021.04.036 © 2021 International Society of Nephrology. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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The management of atypical hemolytic uremic syndrome (aHUS), related to complement alternative pathway dysregulation, has been revolutionized by the use of eculizumab, an anti-C5 blocking monoclonal antibody. C5 blockade is very efficient at reversing hematological abnormalities, associated with an active aHUS process, whether or not an acquired or inherited complement abnormality is identified. More importantly, eculizumab was found to dramatically improve aHUS renal outcomes, irrespective of whether the disease involves native or transplanted kidneys, both in children and adults. A large multicenter study recently showed that the broad use of eculizumab in France has completely changed renal epidemiology of aHUS across the country, allowing to halve the aHUS population on chronic dialysis, over a period of 5 years. Notably, evidence has been accumulating to emphasize the importance of an early-onset treatment to ensure optimal renal function recovery. This therapy is administered twice a month via intravenous infusion, yet requires hospital admission in a daycare facility. The ideal duration of the treatment, based on an individualized risk assessment, as well as the possibility of spacing out eculizumab doses, based on personalized monitoring, are key pending questions that warrant further investigations.

Long-term outcomes were recently reported by Menne et al. Ninety-three patients were enrolled in 5 clinical trials and were given at least 1 eculizumab dose, 51 of whom (55%) were maintained on long-term eculizumab therapy. Among the 42 patients (45%) who discontinued treatment, 21 (50%) had to resume for subsequent aHUS relapse. Interestingly, patients in the relapsing subgroup were more likely to harbor complement abnormalities and had a greater number of prior thrombotic microangiopathy (TMA) events than those in the nonrelapsing group. Furthermore, the “eculizumab re-initiation” group displayed a trend toward hastened decline in renal function. Besides confirming the efficacy of long-term eculizumab therapy at controlling aHUS, this study further established the C5-blockade-related risk of developing a meningococcal infection.

In an attempt to increase the half-life of eculizumab and therefore to extend dosing interval from 2 to 8 weeks, ravulizumab was derived from eculizumab with the change of 4 amino-acids. Ravulizumab was engineered to decrease the affinity of the antibody binding domain for C5 and to augment the affinity of Fc domain for the neonatal Fc receptor (FcRn) at low pH, to promote antibody recycling from the endosomal compartment. Rondeau et al. recently reported the results of a phase 3, single-arm study in complement inhibitor-naïve adults (18 years and older), who fulfilled diagnostic criteria for aHUS. The enrolled patients received ravulizumab through a 26-week initial evaluation period. The primary endpoint was complete TMA response defined as normalization of platelet count and lactate dehydrogenase and 25% or more improvement in serum creatinine. Secondary endpoints included changes in hematologic variables and renal function. Safety was also evaluated. Ravulizumab treatment resulted in an immediate, complete, and sustained C5 inhibition in all patients. Complete TMA response was achieved in 53.6% of patients. Normalization of platelet count, lactate dehydrogenase, and 25% or more improvement in serum creatinine was achieved in 83.9%, 76.8%, and 58.9% of patients, respectively. Finally, treatment with ravulizumab once every 8 weeks resulted in rapidly improved hematologic and renal endpoints with no unexpected adverse events in adults with
atypical hemolytic uremic syndrome.

In the present issue (Figure 1), Barbour et al. reported on long-term efficacy of the long-acting C5 inhibitor, ravulizumab, for the treatment of aHUS in adults, extending the previous 26-week follow-up study. The patients were followed for a median of 76.7 weeks. Forty-nine patients, of the 58 patients enrolled in the initial study, entered the extended follow-up period. Importantly, 4 additional patients achieved complete TMA response. Potent prevention of TMA events, renal function improvement, and better quality of life, under ravulizumab long-term treatment, were further confirmed throughout the study period.

However, the very high cost of eculizumab treatment, as well as the significantly increased risk of meningococcal infection related to C5 blockade have prompted investigators to investigate the safety of eculizumab discontinuation. Fakhouri et al. designed a prospective national multicenter open-label study, meant to evaluate eculizumab withdrawal. Of the 55 children and adults enrolled in the study, aHUS relapse occurred in 13 (23%) of them, throughout the follow-up period. Importantly, 3 main risk factors for relapse were identified, including female gender, presence of a rare complement gene variant, and increased soluble C5b-9 plasma levels at eculizumab discontinuation. Eculizumab was resumed in the 13 patients with aHUS relapse, 11 of whom regained their baseline renal function, whereas 2 of them failed to recover from kidney failure. Treatment withdrawal was overall feasible and safe, at least in a targeted population of non-transplanted patients with aHUS, yet deserves a close monitoring. Together, the studies by Menne et al. and Fakhouri et al. stress the need for tailoring treatment based on an individualized benefit-risk evaluation, according to complement investigations and medical history.

There is no doubt that a long-acting formulation of anti-C5 antibody will improve the quality of life of patients with aHUS on long-term treatment, while ensuring a safety/efficacy balance comparable to that of eculizumab. However, the patents on eculizumab are expected to expire in a near future, providing biosimilar opportunities and giving hope for significant treatment cost reduction. Thus, the key question is whether the gain in quality of life, due to spaced administration, will be considered worth enough to justify the over-cost of ravulizumab over short-acting eculizumab biosimilars. The discussion will be further spiced up by the upcoming availability of new C5 blockers. Nomacopan (coversin) and Zilucoplan are 2 small molecules, with short half-life, that are administered through daily subcutaneous injection. A PASylated coversin is currently developed to extend half-life and allow a weekly subcutaneous dosing regimen. Last but not least, another long-acting anti-C5, named crovalimab, whose engineering is also based on pH-dependent recycling technology, was used in patients with paroxysmal nocturnal hemoglobinuria. Subcutaneous crovalimab administered every 4 weeks provided complete and sustained terminal complex pathway inhibition and suppressed hemolytic activity.

In summary, the development of new complement blockers that could be either injected through intravenous route every other month, or self-administered (subcutaneously), is definitely a stride forward for the quality of life of patients with aHUS patients. However, this broader therapeutic toolbox will also add further complexity to the highly individualized management of patients.
with aHUS, increasingly recognized as a paradigm of precision medicine.

DISCLOSURE

The authors declared no competing interests.

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