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Eculizumab and aHUS: Spotlight on Patient-Centered Care

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Recently, assessment and reporting of patient-centered outcomes has ushered in a new era in clinical research. Nephrology has not trailed behind, as various settings connected to kidney diseases have come under increased scrutiny thanks to the emergence of well-designed specific questionnaires. In this edition, Greenbaum *et al*. address the issue of patient-reported outcomes (PROs) related to eculizumab therapy in the context of atypical hemolytic uremic syndrome (aHUS).[1]

This longitudinal study was spawned by the Global aHUS Registry as an original and collaborative partnership between patients and clinicians committed to a better alignment of clinical research goals with patient needs.[2] Ever since its inception in 2012, this innovative worldwide program, bolstered by industry support, has mustered patient organizations and expert clinicians from 16 countries in a bid to identify and prioritize clinical issues pertaining to aHUS. Given the incidence of aHUS, this registry represents a major initiative designed to circumvent the challenges posed by such a rare disease. Most of all, the novelty of this research model lies in the way in which it incorporates patient participation. From being merely a passive subject, the patient morphs into a key actor directly involved in the design of a research agenda that focuses on their own priorities. From this standpoint, the Global aHUS Registry represents a more than welcome step in the direction of patient empowerment. Patient selection methods, with straightforward inclusion criteria, ensure broad patient enrollment. Notably, identification of a complement gene variant and/or factor H autoantibodies are not prerequisites for patient recruitment, and both adult and pediatric patients can be enlisted.

Over a period of 8 years, the Global aHUS Registry has been built up to become the world's largest dataset of patients with aHUS, engaging with such crucial issues as the natural course of the disease and real-world information on drug safety. As of July 2019, a total of 1811 patients, both children and adults, had been included in the registry. Among its noteworthy achievements, the registry has yielded reassuring results with respect to the safety profile of eculizumab in both the adult and pediatric populations.[3]

Atypical hemolytic uremic syndrome has a great impact on health-related quality of life (HRQoL) not only because of direct clinical consequences (renal, extrarenal complications such as anemia, neurological sequelae, and diabetes in children) but also because of management requirements (such as plasma exchanges, dialysis, or repeated hospitalizations). As evidence of the rising importance of PROs, many agencies now recommend their use along traditional clinical endpoints. Initially, HRQoL scoring outcomes were included as secondary endpoints, specifically in a seminal trial demonstrating the efficacy of eculizumab in aHUS. Various PROs questionnaires have since been used to assess the patient's quality of life before and after eculizumab therapy: EuroQol Five Dimensions Questionnaire (EQ-5D), Visual Analog Scale (VAS), or Functional Assessment of Chronic Illness Therapy—Fatigue (FACIT-F). Based on the Evaluating Measures of Patient Reported Outcomes (EMPRO) assessment, the EQ-5 D scale yielded the most favorable scores and has established itself as the most suitable PRO evaluation tool in the setting of aHUS.[4] In all these studies, eculizumab therapy achieved significant improvements in HRQoL scores very shortly after initiation (within the first week of therapy) with a sustained efficacy in long-term follow-up.[5] The FACIT-F scale is a 13-item questionnaire the main advantage of which is its versatility. It has been validated for evaluating the impact of fatigue on daily activities in numerous

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chronic conditions such as cancer, lupus, and arthritis. In the context of aHUS, it has been tested by the authors in 2 pediatric studies,[6] but has only once been used in an adult study.[7] Of note, results stemming from pediatric investigations may differ greatly from adult results with respect to HRQoL. This has been demonstrated in a study by Werner *et al.*, whereby long-term HRQoL perception was not significantly modified in the subgroup of children affected by aHUS.[8] Keeping these exceptions in mind, evaluation of PROs at different timepoints in the course of the disease and under different treatment conditions has been singularly lacking to date.

The chief finding is that eculizumab significantly improves FACIT-F scores in patients treated with the drug. To reach such a conclusion, the authors draw primarily on the group of patients ($n = 23$) who started eculizumab after enrollment. Nearly 75% of the patients exhibited significant amelioration (FACIT-F score >3) following initiation of the treatment, and the same proportion self-reported "good" to "excellent" general health status. Given that the FACIT-F scores remain stable on follow-up in the "on eculizumab on enrollment" group, it may be further argued that the benefits of eculizumab are sustained over time. Next to highlighting the drug's satisfactory safety profile, the Global aHUS Registry thus adds another milestone by substantiating the claim that anti-C5 therapy translates into an improved quality of life. In particular, this result is likely to address a core concern of any patient (and attending caregiver) on the verge of starting a new treatment.

From the wealth of data provided by this report, 2 observations merit singling out: (i) patients in both the "never on eculizumab" and "on eculizumab" groups yielded unchanged FACIT-F scores throughout the study period, and furthermore, (ii) these scores were roughly similar to those from the general population, as the reviewers candidly admit. Inferences derived from the combination of these results are bound to remain speculative in the absence of statistical analysis. However, they suggest that patients already on eculizumab experience an uneventful course, free from disease recurrence together with stabilized chronic kidney disease, and to such an extent that they enjoy a quality of life akin to that of the general population. The group "never on eculizumab" poses a different challenge with respect to the interpretation of these results. One may argue that this group is a selected subset of patients deemed less vulnerable to disease recurrence, progression, subsequent hospital admission, and repeated treatments, hence their favorable FACIT-F scores. Taken together, these results stress the importance of careful evaluation of eculizumab therapy indication, as patients without anti-C5 therapy seem to fare as well overall as treated patients.

The authors also produce a comprehensive overview of symptoms reported by patients, from which different patterns emerge. Anxiety appears to be a frequent complaint shared by more than one-third of the cohort taken as a whole and one-half of the patients from the subset started on eculizumab during follow-up. In this latter group, eculizumab therapy initiation did not translate into a significant reduction of anxiety. Headache ranked as the most prevalent symptom reported by more than 50% of the study population, irrespective of their status regarding eculizumab. In view of its detrimental effects on PROs, this result invites further inquiry. It may be posited that the relationship between aHUS and headaches could be related to small-vessel ischemia in the brain resulting from thrombotic microangiopathy, or to hypertension related to chronic kidney disease and/or aHUS. However, causation is far from obvious, bearing in mind the high prevalence of headaches in the general population. Accordingly, a recent study showed no significant difference in a standardized headache score (HIT-6) between recovering aHUS patients and sex-matched controls. At variance, patients recovering from thrombocytopenic thrombotic purpura displayed significantly increased headache scores.[9]

These findings provide leverage for targeted interventions that may further ameliorate the patient's well-being. Anxiety is tied up with numerous somatic complaints depicted in the study, such as weakness and fatigue, and its burden on patients is well recognized. Therefore, the timely recognition of this symptom, together with its appropriate specialized management, is bound to provide significant relief to patients.

Besides the inherent biases associated with self-reporting, the study suffers from several limitations. First and foremost is the small sample size of the main analysis group, the subset of patients who were started on eculizumab after enrollment. This meant that an adjusted statistical model that would account for potential confounders was not deemed practical. One such confounder likely to have an impact on FACIT-F scores is kidney function. Subgroup analysis according to renal status (dialysis,

transplantation, and no dialysis) was thus subsequently performed to address this issue. At first glance, it produced seemingly favorable and consistent results across the various subgroups, further confirming the positive effects of eculizumab. Nonetheless, group size greatly reduces its meaningfulness.

In the same vein, this group included only 3 pediatric patients, so that it precludes any definitive conclusion regarding this age category. Between-group statistical comparisons involving the 3 predefined categories "never on eculizumab" "on eculizumab on enrollment" and "eculizumab initiated after enrollment" were not performed. When it comes to quality-of- life—related variables, in-between group comparisons are notoriously challenging. Nevertheless, it would have been useful to compare the "eculizumab initiated after enrollment" to the 2 other reference groups to gauge even more accurately the effects of anti-C5 therapy. However, partly because prespecified hypotheses were not developed, it was impossible to perform such comparisons.

Notwithstanding these limitations, the study by Greenbaum *et al*. offers meaningful clinical cues for future clinical investigation. Most of all, it provides further proof of the benefits of eculizumab therapy. Provided that anti-C5 treatment is initiated on valid grounds, eculizumab offers the patient significant alleviation of symptoms. Uniquely, the evidence comes not from what patients may perceive as cryptic data or outcomes disconnected from their genuine concerns, but instead relies on real-world data reported by the patients themselves.

DISCLOSURE

YL and CR have received lecture fees from Alexion pharmaceuticals. CR has received travel grants from Alexion pharmaceuticals.

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