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Incorporating Patient-reported Outcomes into HCV Treatment Studies

Donna M. Evon, Ph.D.

The FDA's definition of a Patient-Reported Outcome (PRO) as "any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else" is now widely accepted by investigators¹. "PRO" has become an umbrella term that includes any outcome directly reported by patients that captures their subjective experience of phenomena that cannot be captured through other means. The most commonly reported PROs are health-related quality of life (HrQOL), physical and mental symptoms and side effects, and functional status related to a disease, procedure or treatment. However, PROs are also any other patient-reported data not easily captured via clinician-report or objective marker and can include other psychosocial experiences (e.g., perceived stigma, motivation for treatment), access to and satisfaction with care, perceived treatment benefits or harms, adverse events, behaviors, and treatment adherence².

PROs can be measured using numerous modalities including single item questions about a simple concept to lengthier assessments of multi-faceted constructs, such as HrQOL which has been the hallmark of numerous PRO endeavors. PROs often capture patients' experiences before, during and after clinical procedures, treatments or interventions to evaluate treatment benefits and harms. In other medical fields, such as oncology, PROs have become respected and valuable endpoints of clinical studies equally as important as hard endpoints such as mortality³. There is no disputing the fact that biomedical endpoints, such as a sustained virological response (SVR) or extending life years are prominent and salient endpoints; of course projected cure rates are critical to our patients. However it would be short-sighted to assume that SVR is the only factor that matters to patients. Each individual comes to clinic with their own preferences, values, and concerns related to trade-offs between multiple outcomes (e.g., cure rates, treatment durations, side effects, and functional status). Therefore, PRO studies provide complementary information about additional benefits and harms that matter to patients. Discussion of such issues between patients and

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Corresponding Author: Donna M. Evon, Ph.D., Associate Professor, Licensed Clinical Psychologist, Director of Psychosocial Services and Research, Division of Gastroenterology and Hepatology, CB# 7584, 8010 Burnett-Womack, University of North Carolina, Chapel Hill, NC 27599, donna_evon@med.unc.edu.

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providers can add enormous value to the decision-making process, patient satisfaction, and healthcare quality.

Younossi and colleagues are to be congratulated on investigating critically important PROs published in this issue of *Clinical Gastroenterology and Hepatology*⁴, just seven months following the main NEUTRINO and FUSION papers published in *The New England Journal of Medicine* in May 2013^{5, 6}. The comparative analysis of key PROs between interferon (IFN)-containing and IFN-free regimens is extremely timely given that thousands of patients and providers are presently weighing the pros and cons and various trade-offs of multiple treatment regimens now available in clinical practice.

Younossi et al., utilized data derived from two large pharmaceutical Phase III trials (FUSION, NEUTRINO)^{5, 6} to examine differences in PROs between patients treated with an all-oral IFN-free regimen (ribavirin (RBV) + sofosbuvir (SOF)) and those treated with an IFN-containing regimen (IFN+ RBV+SOF)⁴. Participants in FUSION (N=201) were infected with genotype 2 or 3, had been previously treated with PEGIFN/RBV, and received RBV+SOF for 12 or 16 weeks. Participants in NEUTRINO (N=327) were infected with genotype 1, were treatment naïve, and received PEGIFN+RBV+SOF for 12 weeks. PRO measures with well-established psychometric properties, including the Chronic Liver Disease Questionnaire, Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F), and the Work Productivity and Activity Index, were administered in both trials at baseline, during treatment, at the end of treatment, and up to 12 weeks post-treatment in patients who achieved SVR.

Compared to baseline, participants reported clinically significant worsening of fatigue, health functioning, and work-related productivity during *both* IFN-free and IFN-containing regimens. While it was not surprising that patients on IFN-containing regimens exhibited more challenges compared to those on IFN-free regimens, the finding that patients on the IFN-free regimen still exhibited worsening of these PROs is highly noteworthy, and underscores the need for providers to consider these findings when deliberating about treatment options and to communicate these findings to patients to ensure that they are making informed treatment decisions. Patients and providers will also benefit from knowing that these particular PROs improve and return to baseline more rapidly after IFN-free regimens, but may linger for weeks or months after IFN-containing regimens. Beneficial improvements in fatigue, functional status, and work productivity were reported by patients who achieved SVR, regardless of which treatment regimen was prescribed, with some scores improving beyond baseline values.

Results also demonstrated that major predictors of worsening of these PROs were anxiety, depression, fatigue, female gender and cirrhosis; higher fatigue was associated with lower functional status and work productivity, after controlling for depression, anxiety and cirrhosis. These findings suggest that pharmacological and cognitive-behavioral interventions are sorely needed to target the mental health and well-being of individuals infected with HCV. The strengths of Younossi et al.'s study are numerous: it is the first longitudinal study comparing PROs during and after IFN-free and IFN-containing regimens, use of large sample sizes, and use of well-validated instruments. As the authors described

well, their study findings were limited by baseline differences between the trial cohorts, lack of follow-up data for patients who did not achieve SVR, and lack of generalizability of the results of this study to dissimilar patient populations and treatment settings. These limitations notwithstanding, this study sets the stage for future PRO measurements in Phase II or III clinical trials and comparative effectiveness studies in more diverse patients undergoing therapy during standard “real world” clinical care⁷.

While Younossi et al.’s paper blazed the trail for inclusion of PRO measures in clinical trials of new DAA –based regimens, many other key questions remain unanswered and need to be examined to paint a complete picture for patients and other stakeholders involved in treatment decisions. In a mixed methods interview pilot study recently conducted among 45 HCV patients contemplating treatment, our preliminary findings demonstrated informational needs patients identified as their top priorities. These include not only SVR rates and short and long term effects of treatment on liver and other pre-existing conditions, but also many factors that would require PRO assessments, such as: symptom and functional improvement after treatment, interference with quality of life and functional status at work and with family/home-based activities, treatment side effects, out-of-pocket costs; and logistical details about duration and frequency of treatment visits (unpublished data). Younossi et al.’s study provides initial answers to some of these priority questions by providing information regarding the impact of SOF+RBV treatment and achieving SVR on fatigue, functioning, and work productivity. More comparative effectiveness patient-centered research is needed particularly in diverse populations afflicted with multiple comorbidities⁷. There is also a pressing need to identify uncommon but irreversible treatment harms that may emerge with wider use of DAA-based therapy in long-term observational studies that employ PRO measures⁷⁻⁹.

Researchers contemplating using PROs as primary or secondary endpoints should be familiar with the NIH-funded initiative “Patient-Reported Outcomes Measurement Information System,” commonly referred to as PROMIS (<http://www.nihpromis.org/>). PROMIS provides researchers access to a comprehensive set of highly reliable, validated, precise tools that measure health constructs and symptoms across a wide range of chronic medical conditions. PROMIS also features an Assessment Center, a free, online data collection tool that allows researchers to create study-specific websites, capture data electronically from patients, verify data integrity, store protected health information, and export to statistical software (<http://www.assessmentcenter.net/>). The development of new PRO measures specifically for HCV and antiviral therapy is burgeoning and warrants consideration for future PRO studies as well^{10, 11}.

The importance of PROs to capture the patient’s perspective has played an enormous role in a recent movement to stimulate more patient-centered outcomes research (PCOR) as epitomized by the massive government backing of the Patient Centered Outcomes Research Institute (PCORI; www.pcori.org). Established and dictated by Congress as part of the Patient Protection and Affordable Care Act of 2010, this independent, non-federal health research organization, has been developed to stimulate and fund comparative effectiveness research that is patient-centered, requiring patient engagement at every step in the research process, from prioritizing top research topics, to designing studies, to dissemination of

findings to the lay public. Needless to say, PROs, which are inherently patient-centered, are frequently chosen as the primary or secondary study endpoints, therefore PCORI offers a unique opportunity to fund PCOR related to HCV treatment.

Where should we go from here with PROs as part of antiviral therapy research?

- a. PROs should be included in long-term observational or randomized trials of a more diverse range of patients treated in standard clinical practice to conduct patient-centered comparative effectiveness research and address several of the pressing research questions related to newer DAA-based therapy⁷.
- b. Development of PRO guidelines and recommendations for use in HCV antiviral therapy research, similar to standards established for oncology trials could improve scientific rigor and comparability across studies¹².
- c. Collection and feasibility of PRO measures through electronic medical records is occurring in other medical arenas¹³ and could be implemented for HCV therapy in large U.S. healthcare systems.
- d. National research networks and clinical data registries, such as HCV-TARGET (<http://www.hcvtarget.org/>), that collect biomedical endpoints can be easily expanded to include PRO measurement.
- e. Key stakeholders should strive to publish PRO results of clinical trials alongside the main efficacy paper, in a separate, complementary report, as is done in other medical arenas^{3, 14}. Three years after boceprevir and teleprevir were approved, only one PRO study has been published. Simultaneous publication of PRO results would elevate the stature of PROs to a level similar to SVR or other study endpoints and provide consumers with more immediate and comprehensive data on which to make more informed decisions.

Multiple treatment options will soon confer uniformly high SVR rates. However, cure rate is just one feature that patients care about when considering treatment. Decisions about treatment options may be based more upon patient preferences regarding other treatment outcomes and a significant portion of these outcomes need to be obtained through direct patient reporting. Investigations such as those by Younossi et al. provide patients, providers, and other key stakeholders with important information on other relevant treatment issues. PRO studies will be of paramount importance when SVR no longer drives the decision-making process.

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