Hepatitis C in Young Children: To Treat or Not to Treat – Is It Cost-Effective?

Chronic hepatitis C virus (HCV) infection, one of the most important public health problems in modern medicine, is responsible for approximately 71 million infections worldwide. The global disease burden of children with HCV infection aged 0-18 years is estimated to be 0.13%, corresponding with 3.26 million children.[1] In 2018, the prevalence of children with HCV infection in the US and Europe was estimated to be 0.05%-0.36%.[2]

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The evolution of HCV treatment has progressed rapidly since the identification of the virus in 1989. The development of highly effective and well-tolerated direct-acting antiviral (DAA) agents have significantly improved cure rates, which is an important step toward the eradication of chronic HCV infection.[3] Similar to their adult counterparts, studies evaluating the efficacy and safety of DAA in children have shown excellent results and relatively minor side effects.[4-6] The US Food and Drug Administration has approved DAA agents for children as young as 3 years of age with genotypes 1, 4, 5, or 6 infection and for children aged 6 to less than 18 years with any HCV genotype regardless of presence of cirrhosis or history of previous treatment. However, these drugs are expensive and can substantially impact the budget of private and government payers.[7,8] Therefore, cost is becoming the primary barrier for the treatment of HCV at young age. In this volume of *The Journal*, Greenaway et al[9] address the cost-effectiveness of early treatment of young children with chronic HCV with new DAA therapy.

Greenaway et al created a state transition model to assess the cost effectiveness of treating a hypothetical cohort of 10 000 children with chronic HCV at age 6 years with combination therapy of sofosbuvir/ledipasvir for 12 weeks vs deferring treatment until 18 years of age. The goal of treatment was sustained virologic response, defined as undetectable serum level of HCV RNA 12 weeks after completion of therapy (sustained virologic response at 12 weeks [SVR 12]). The authors set uniform characteristics for the patients in the model: HCV genotype 1, perinatal transmission, no comorbidities, no spontaneous remission, no fibrosis at the initiation of treatment, complete treatment uptake, regression of liver damage after successful treatment, 1-time treatment, and no reinfection. Cost and health outcomes were measured using total medical costs, quality-adjusted life-years (QALYs), and incremental cost-effectiveness ratios. The QALY reflects both the quantity and the quality of life. One QALY equates to 1 year in perfect health. The cost-effectiveness ratio represents a measure of how efficiently the proposed intervention can produce an additional QALY.[10]

The authors demonstrated that the incremental cost effectiveness of early treatment of young children was $12 690 per QALY gained after 20 years, which is considered cost effective compared with deferred treatment. As a general rule, interventions with lower cost per QALY gained are reasonably efficient. For this analysis, the authors used a threshold of cost-effectiveness value of $50 000 per QALY, which is conservative for the US, but it is the threshold of cost effectiveness generally accepted in Canada.[11] For the US, the most commonly cited thresholds are those used by the Institute for Clinical and Economic Review and range between $50 000 and $150 000 per QALY.[12] Their analysis showed that even using the lowest threshold ($50 000 per QALY), treating children at age 6 years still constitutes a good value for money. If one were to choose a higher threshold, then this conclusion becomes stronger. Using higher thresholds of $100 000 to $150 000 per QALY show that early treatment would be even more cost effective.

An important aspect of this study is that authors also conducted a threshold analysis to see how low the future drug cost would have to be so that administering the drug early would exceed the $50 000 per QALY threshold. They determined that if the cost of DAA medications is reduced by 60% in 12 years, then deferring treatment until adulthood would be the most cost-effective option. However, they also demonstrated that delaying treatment until adulthood can result in significant complications, such as the development of cirrhosis, hepatocellular carcinoma, and death related to liver disease.

The investigators presented an additional scenario treating children as young as 3 years of age and using alternative treatment with the pan-genotypic combination of glecaprevir/pibrentasvir for 8 weeks. They reported an incremental cost effectiveness of $12 497 per QALY; using glecaprevir/pibrentasvir resulted in an incremental cost effectiveness of $12 563 per QALY compared with deferring treatment to age 18 years. The data reflects that both treatment options, starting treatment at age 3 years and using pangenotypic DAA, are cost effective.

There is a paucity of data regarding cost-effectiveness studies in children with HCV infection. Nguyen et al showed that treating a hypothetical cohort of 30 000 children with

DAA	Direct-acting antiviral
HCV	Hepatitis C virus
QALY	Quality-adjusted life-year

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chronic HCV with DAA at age 12 years compared with deferring treatment until adulthood is cost effective.[13] They used a novel approach to demonstrate that DAA therapies are an important tool in the management of HCV in children. Greenaway et al[9] took this subject to a new level. They evaluated cost-effectiveness of treatment at a younger age (6 years) while incorporating fibrosis progression rates specific to children with HCV infection in their analysis.

Finally, the authors contribute to the debate of whether to treat or defer treatment for hepatitis C in young children based only on medication cost. Commercial and government insurance companies prioritize treatment based on fibrosis stage in which treatment is approved for patients with advanced fibrosis.[14] In pediatric patients, especially at young ages, the likelihood of advanced fibrosis is minimal.[15] However, current recommendations for the management of HCV state that children should be treated regardless of fibrosis stage once an acceptable treatment regimen is available.[16,17]

The impact of HCV infection in health-related quality of life also needs to be taken into consideration when making decisions regarding initiation or deferment of treatment in young children. Several studies have demonstrated the significant impairment on quality of life, psychosocial health, and cognitive functioning in children with HCV infection. The presence of HCV infection is also a source of distress for the caregivers of these children.[18,19] However, after treatment and eradication of the virus, these areas rapidly improve. Younossi et al[20] reported significant improvement of quality of life in adolescents with HCV infection treated with DAA agents. Another argument about offering treatment to young children is the use of lower and therefore cheaper doses of DAA agents as compared with adults which can result in potential cost savings.[16]

In summary, the use of DAA therapy is cost effective in the pediatric population and medical decisions for this treatment should not be based solely on economic reasons. All children deserve fair access to a cure for HCV. ■

Norberto Rodriguez-Baez, MD
Department of Pediatrics
University of Texas Southwestern Medical Center
Dallas, TX

Reprint requests: Norberto Rodriguez-Baez, MD, Department of Pediatrics, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd, Dallas, TX 75390. E-mail: norberto.rodriguez-baez@utsouthwestern.edu

References

1. Schmelzer J, Dugan E, Blach S, Coleman S, Cai Z, DePaola M, et al. Global prevalence of hepatitis C virus in children in 2018: a modelling study. Lancet Gastroenterol Hepatol 2020;5:374-92.
2. El-Shabrawi MH, Kamal NM. Burden of pediatric hepatitis C. World J Gastroenterol 2013;19:7880-8.
3. Dahiya M, Hussaini T, Yoshida EM. The revolutionary changes in hepatitis C treatment: a concise review. B C Med J 2019;61:72-7.
4. Rosenthal P, Schwarz KB, Gonzalez-Peralta RP, Lin CH, Kelly DA, Nightingale S, et al. Sofosbuvir and Ribavirin therapy for children aged 3 to <12 years with hepatitis C virus genotype 2 or 3 infection. Hepatology 2020;71:31-43.
5. Schwarz KB, Rosenthal P, Murray KF, Honegger JR, Hardikar W, Hague R, et al. Ledipasvir-sofosbuvir for 12 weeks in children 3 to <6 years old with chronic hepatitis C. Hepatology 2020;71:422-30.
6. Jonas MM, Squires RH, Rhee SM, Lin CW, Bessho K, Feiterna-Sperling C, et al. Pharmacokinetics, safety, and efficacy of glecaprevir/pibrentasvir in adolescents with chronic hepatitis c virus: part 1 of the DORA study. Hepatology 2020;71:456-62.
7. Rein DB, Wittenborn JS, Smith BD, Liffmann DK, Ward JW. The cost-effectiveness, health benefits, and financial costs of new antiviral treatments for hepatitis C virus. Clin Infect Dis 2015;61:157-68.
8. Rein DB, Smith BD, Wittenborn JS, Lesesne SB, Wagner LD, Roblin DW, et al. The cost-effectiveness of birth-cohort screening for hepatitis C antibody in U.S. primary care settings. Ann Intern Med 2012;156:263-70.
9. Greenaway E, Haines A, Ling SC, Krahn M. Treatment of chronic hepatitis C in young children reduces adverse outcomes and is cost-effective compared to deferring treatment to adulthood. J Pediatr 2021;230:38-45.
10. Kirkdale R, Krell J, O'Hanlon Brown C, Tuthill M, Waxman J. The cost of a QALY. Q J Med 2010;103:715-20.
11. Neumann PJ, Cohen JT, Weinstein MC. Updating cost-effectiveness–the curious resilience of the $50,000-per-QALY threshold. N Engl J Med 2014;371:796-7.
12. Institute for Clinical and Economic Review. Final value assessment framework for 2017-2019. https://icer-review.org/final-vaf-2017-2019/. Accessed September 26, 2020.
13. Nguyen J, Barritt AS, Jhaveri R. Cost effectiveness of early treatment with direct-acting antiviral therapy in adolescent patients with hepatitis C virus infection. J Pediatr 2019;207:90-6.
14. Squires JE, Balistreri WF. Hepatitis C virus infection in children and adolescents. Hepatol Commun 2017;1:87-98.
15. Guido M, Bortolotti F, Leandro G, Jara P, Hierro L, Larrauri J, et al. Fibrosis in chronic hepatitis C acquired in infancy: is it only a matter of time? Am J Gastroenterol 2003;98:660-3.
16. Indolfi G, Hierro L, Dezsofi A, Jahnel J, Debray D, Hadzic N, et al. Treatment of chronic hepatitis C virus infection in children: a position paper by the Hepatology Committee of European Society of Paediatric Gastroenterology, Hepatology and Nutrition. J Pediatr Gastroenterol Nutr 2018;66:505-15.
17. Leung DH, Squires JE, Jhaveri R, Kerkar N, Lin C-H, Mohan P, et al. Hepatitis C in 2020: a North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition position paper. J Pediatr Gastroenterol Nutr 2020;71:407-17.
18. Nydegger A, Srivastava A, Wake M, Smith AL, Hardikar W. Health-related quality of life in children with hepatitis C acquired in the first year of life. J Gastroenterol Hepatol 2008;23:226-30.
19. Rodrigue JR, Balistreri W, Haber B, Jonas MM, Mohan P, Molleston JP, et al. Impact of hepatitis C virus infection on children and their caregivers: quality of life, cognitive, and emotional outcomes. J Pediatr Gastroenterol Nutr 2009;48:341-7.
20. Younossi ZM, Stepanova M, Balistreri W, Schwarz K, Murray KF, Rosenthal P, et al. Health-related quality of life in adolescent patients with hepatitis C genotype 1 treated with sofosbuvir and ledipasvir. J Pediatr Gastroenterol Nutr 2018;66:112-6.