Direct-acting antiviral treatments in Australia for children with chronic hepatitis C virus infection

Jessica A Eldredge[1], Michael O Stormon[2,3], Julia E Clark[4,5], Scott Nightingale[6,7], Brendan McMullan[8,9], Brooke Andersen[2], Christina Travers[4], Winita Hardikar[1,10]

Three and one-half million children around the world have chronic hepatitis C virus (HCV) infection.[1] In Australia, the prevalence is estimated to be at least 0.4 cases per 100 000 children under 15 years of age.[2] Chronic hepatitis C in children can have an indolent course, but can progress to hepatic fibrosis, chronic liver disease, and hepatocellular cancer. These often marginalised children experience reduced quality of life, social stigmatisation, and inadequate access to specialist care in Australia.[3,4] Early treatment of HCV in children is cost-effective and reduces the lifetime impact of chronic liver disease and its sequelae.[5]

Direct-acting antiviral (DAA) treatments have revolutionised the management of HCV infection. In April 2020, age restrictions were removed for three fixed dose DAA preparations subsidised in Australia by the Pharmaceutical Benefits Scheme (PBS).[4]

We examined outcomes for children under 18 years of age with HCV infection treated with DAAs during 1 April 2018 – 1 April 2022 at five tertiary children's hospitals (Royal Children's Hospital, Victoria; Children's Hospital at Westmead, Sydney Children's Hospital Randwick, and John Hunter Children's Hospital, New South Wales; and the Queensland Children's Hospital). Cases were identified by retrospective medical record review of all children treated for hepatitis C during the study period. Sustained viral response was defined as HCV RNA not being detectable by polymerase chain reaction twelve weeks or more after treatment completion (SVR12). Our study was approved by the human research ethics committee of the Royal Children's Hospital, Melbourne (HREC/75391/RCHM-2021).

Fifty-four children with HCV infection commenced DAA treatment at the five participating hospitals during the study period: 32 received glecaprevir/pibrentasvir, eleven ledipasvir/sofosbuvir, ten sofosbuvir/velpatasvir, and one child received sofosbuvir and ribavirin. Eight children commenced DAA treatment prior to April 2020 (with local institutional drug committee approval, compassionate access, or clinical trial participation), 46 after age restrictions were removed in April 2020.

None of the children had received previous treatments for HCV infection. None had documented cirrhosis based on clinical, biochemical, or biopsy assessment by their treating specialists, but liver biopsy identified early fibrosis in one child (carrier of the genetic mutation for alpha-1 antitrypsin deficiency). Four children had foetal alcohol spectrum disorder, and nine patients were Aboriginal or Torres Strait Islander people. Perinatal viral transmission was suspected in 51 cases (Box).

Two children could not be followed up, and one did not complete treatment because of difficulty swallowing the DAA tablet. Fifty of the fifty-one children who completed treatment and were followed up had achieved SVR12; the one child with viraemia reported problems with adherence to therapy because of difficulty swallowing the tablet. The median alanine transaminase (ALT) level declined from 53 U/L (interquartile

Demographic and baseline biochemistry characteristics of 54 children under 18 years of age who commenced direct-acting antiviral treatment for chronic hepatitis C virus (HCV) infections at five Australian children's hospitals, 1 April 2018 – 1 April 2022

Characteristic	Value
Children who commenced treatment	54
Age (years), median (IQR)	12 (9–13)
Sex (boys)	27 (50%)
Weight (*z*-score), median (IQR)*	0.9 (0.2–1.3)
Body mass index (*z*-score) median (IQR)*	0.8 (0.1–1.2)
Ethnic background	
European	25 (46%)
Aboriginal or Torres Strait Islander	9 (16%)
Asian	6 (11%)
Other	3 (6%)
Unknown	11 (20%)
Comorbid conditions	
Neurological/behavioural	
Fetal alcohol syndrome	4 (7%)
Attention disorder/hyperactivity disorder	4 (7%)
Autism	3 (6%)
Other†	3 (6%)
Known hepatic disease‡	2 (4%)
Mode of transmission	
Perinatal transmission	51 (95%)
Injecting drug use	3 (6%)
HCV genotype	
1a	26 (48%)
1b	6 (11%)
3	16 (30%)
4, 5, 6	5 (9%)
Unknown	1 (2%)
Baseline biochemical values prior to treatment: median (IQR)	
HCV RNA detected by polymerase chain reaction (IU/mL)	567 475 (164 500–3 050 000)
Alanine transferase (reference range: 0–35 U/L)	53 (32–79)

Continues

[1] Royal Children's Hospital, Melbourne, VIC. [2] The Children's Hospital at Westmead, Sydney, NSW. [3] The University of Sydney, Sydney, NSW. [4] Queensland Children's Hospital, Brisbane, QLD. [5] The University of Queensland, Brisbane, QLD. [6] John Hunter Children's Hospital, Newcastle, NSW. [7] The University of Newcastle, Newcastle, NSW. [8] Sydney Children's Hospital Randwick, Sydney, NSW. [9] University of New South Wales, Sydney, NSW. [10] The University of Melbourne, Melbourne, VIC. jessica.eldredge@rch.org.au • doi: 10.5694/mja2.51852

Demographic and baseline biochemistry characteristics of 54 children under 18 years of age who commenced direct-acting antiviral treatment for chronic hepatitis C virus (HCV) infections at five Australian children's hospitals, 1 April 2018 – 1 April 2022 (continued)

Characteristic	Value
Platelet count (reference range: 150–400 × 10^9/L)	316 (270–363)
Albumin (reference range: 33–47 g/L)	42 (40–44)
Bilirubin (reference range: 0–15 μmol/L)	8 (5–13)

IQR = interquartile range. * *z*-score: standard deviations from median growth parameter for age, based on Centers for Disease Control standardised growth charts.[6] † Depression, anxiety, cerebral palsy, epilepsy. ‡ Obesity, metabolic associated fatty liver disease, or fibrosis (liver biopsy). ◆

range, [IQR], 32–79 U/L) before to 18 U/L (IQR, 14–24 U/L) after treatment, a clinically significant improvement.

DAA treatments were well tolerated and highly effective in children with HCV infections at five Australian hospitals, consistent with their efficacy in children and adolescents in clinical trials.[7] Adherence to therapy is important when treating younger children; granule preparations may provide greater flexibility and enhance adherence by such patients.

The World Health Organization has set the ambitious target of eradicating HCV globally by 2030.[8] It has recently been projected that only 72% of Australians (all ages) with chronic HCV infection will be treated by this time point.[9] Screening infants and children at particular risk should be the priority, with a focus on early referral to tertiary specialists with experience in treating HCV infection in children. Treating infected Australians early in life will minimise the risk of their lost to medical follow-up, reducing liver-related morbidity, social stigmatisation, and the risks of vertical and horizontal viral transmission prior to adolescence, when activities that increase hepatitis C infection risk increase.

In summary, we found that the benefits of DAA therapy for children with HCV infection are now attainable in Australia in normal practice (ie, outside clinical trials). This can be achieved using standard oral preparations, as outlined in the recent Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine guidelines.[7]

Acknowledgements: We thank all clinicians involved in the care of children treated at the participating hospitals.

Competing interests: No relevant disclosures. ■

Received 23 October 2022, accepted 25 January 2023

1 Indolfi G, Easterbrook P, Dusheiko G, et al. Hepatitis C virus infection in children and adolescents. *Lancet Gastroenterol Hepatol* 2019; 4: 477-487.

2 Raynes-Greenow C, Polis S, Elliott E, et al. Childhood hepatitis C virus infection: an Australian national surveillance study of incident cases over five years. *J Paediatr Child Health* 2015; 51: 1115-1120.

3 Nydegger A, Srivastava A, Wake M, et al. Health-related quality of life in children with hepatitis C acquired in the first year of life. *J Gastroenterol Hepatol* 2008; 23: 226-230.

4 Nightingale S, Stormon MO, Day AS, et al. Chronic hepatitis B and C infection in children in New South Wales. *Med J Aust* 2009; 190: 670-673. https://www.mja.com.au/journal/2009/190/12/chronic-hepatitis-b-and-c-infection-children-new-south-wales

5 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: 90-96.

6 National Center for Health Statistics (Centers for Disease Control and Prevention). CDC growth charts: Z-score data files. Aug 2009. https://www.cdc.gov/growthcharts/zscore.htm (viewed Jan 2023).

7 Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine HCV in children: Australian commentary on AASLD-IDSA guidance. Oct 2021. https://www.hepcguidelines.org.au/wp-content/uploads/2021/11/HCV_in_Children_Guidance_Final_Nov2021.pdf (viewed Jan 2023).

8 World Health Organization. Global health sector strategy on viral hepatitis 2016–2021: towards ending viral hepatitis. June 2016. https://apps.who.int/iris/handle/10665/246177 (viewed Jan 2023).

9 Scott N, Sacks-Davis R, Wade AJ, et al. Australia needs to increase testing to achieve hepatitis C elimination. *Med J Aust* 2020; 212: 365-370. https://www.mja.com.au/journal/2020/212/8/australia-needs-increase-testing-achieve-hepatitis-c-elimination ■