

Minimal monitoring is a safe but underutilised strategy for hepatitis C virus management in Singapore

Dear Editor,

Chronic hepatitis C virus (HCV) infection is estimated to affect 57 million people globally.¹ Despite the availability of safe and effective pan-genotypic direct-acting antivirals,²⁻⁵ many countries have yet to achieve the WHO goal of HCV elimination by 2030.¹ To facilitate HCV elimination, current guidelines recommend using a minimal monitoring (MM) strategy with pan-genotypic direct-acting antiviral (DAA) to streamline HCV treatment.⁶ By minimising the need for extensive laboratory testing and clinic visits, the MM strategy may improve treatment adoption, improve treatment compliance and reduce healthcare costs.⁷⁻⁹ However, the real-world safety, efficacy and uptake of the MM strategy remain limited.

Here, we examined the practical implementation and evaluated the safety and efficacy of the MM strategy compared to the current standard of care (SOC) in Singapore.

Using a prospectively maintained HCV treatment registry, we studied consecutively treated HCV patients with pan-genotypic DAA (either sofosbuvir/velpatasvir or glecaprevir/pibrentasvir), from January 2019 to November 2021 in the Department of Gastroenterology and Hepatology, Changi General Hospital, Singapore. We assessed the eligibility for MM strategy based on the 2019 American Association for the Study of Liver Diseases–Infectious Diseases Society of America (AASLD–IDSA) guideline, specifically treatment-naïve HCV patients without prior liver decompensating events. We considered patients ineligible for MM when they had hepatitis B virus (HBV) or human immunodeficiency virus (HIV) co-infection, known or suspected hepatocellular carcinoma (HCC), prior liver transplantation, or end-stage renal disease.

Typically, all patients have baseline laboratory investigations and a recent ultrasound hepatobiliary system performed within 3 months of the first visit to exclude liver cancer and decompensated cirrhosis. Fibrosis staging was performed using a combination of FIB-4 score and vibration-controlled transient elastography. Amid the COVID-19 pandemic, some physicians adopted the MM strategy due to resource constraints in our institution. For patients deemed suitable for MM, DAA will be initiated at the first visit and reviewed during a check for sustained

virological response 12 weeks after treatment completion (SVR12). Patients in the MM group were instructed to self-monitor for potential drug-related adverse events. MM-monitored patients had only 2 visits from DAA initiation to SVR12 at our institution. Patients with additional outpatient visits between DAA initiation and SVR12 were classified as SOC-monitored. There is no protocol for teleconsultation or review by nurses between DAA initiation and SVR12.

The study aimed to investigate 2 outcomes: (1) serious adverse events (SAE), which were defined as adverse events resulting in early cessation of HCV treatment, hospital admissions, permanent disability or death, and (2) SVR12.

The study verified treatment compliance using both medical records and pharmacy databases. Statistical analysis was performed using SPSS version 23.0 (IBM Corp, Armonk, NY, US). The study adhered to the Declaration of Helsinki, and the institutional review board granted a waiver of consent.

The final analysis included a total of 608 HCV patients, with the majority being male (90.8%) and treatment-naïve (97.7%). Among them, 60.2% had genotype 3 infections, 18.7% had cirrhosis at baseline, and 2% had co-infection with either HBV/HIV infection. Among the patients, 7.9% (n=48) were not eligible for MM due to being either treatment-experienced (2.3%), having decompensated cirrhosis (2.1%), HCC (1.3%), HBV/HIV co-infection (2.0%), or end-stage renal disease (0.3%).

While 92.1% (n=560) were eligible for MM, only 12.5% (n=70) were monitored with the MM strategy (Table 1). Among patients eligible for MM, the baseline demographics were similar between MM and SOC groups, except that the MM group was older (54 versus 50 years, $P=0.0006$). The overall SVR12 was 92.8%, which was similar between MM and SOC monitoring (92.9% vs 92.7%, $P=0.952$). Compared to those who underwent SOC monitoring, patients monitored with MM had similar treatment completion rates (100% vs 96%, $P=0.093$) and treatment compliance rates (95.7% vs 95.3%, $P=0.882$). Moreover, the MM group had significantly fewer clinic visits than the SOC group—the median number (interquartile range [IQR]) of clinic visits between MM and SOC was (MM: 2 [IQR: 2-2] vs 3 [IQR: 3-3], Mann-Whitney U test;

Table 1. Baseline characteristics of HCV patients eligible for MM (n=560).

	Minimal monitoring (n=70)	Standard of care (n=490)	P value
Baseline characteristics			
Age, mean (SD), years	53.5 (9.7)	50.0 (10.0)	0.0062
Male, no. (%)	65 (92.9)	441 (90.0)	0.442
Race, no. (%)			0.551
Chinese	4 (5.7)	84 (17.1)	
Malay	49 (70.0)	335 (68.4)	
Indian	12 (17.1)	58 (11.8)	
Others	5 (7.1)	13 (2.7)	
Smoker	19 (27.1)	115 (23.5)	0.510
Incarceration	62 (88.6)	419 (85.5)	0.486
HCV genotype, no. (%)			0.402
1	16 (22.9)	104 (21.2)	
2	0 (0.0)	4 (0.8)	
3	38 (54.3)	301 (61.4)	
4	1 (1.4)	0 (0.0)	
5	0 (0.0)	0 (0.0)	
6	0 (0.0)	1 (0.2)	
Not done	15 (21.4)	80 (16.3)	
Fibrosis stage, no. (%)			0.823
0	7 (10.0)	56 (11.4)	
1	13 (18.6)	97 (19.8)	
2	4 (5.7)	48 (9.8)	
3	5 (7.1)	33 (6.7)	
4	7 (10.0)	61 (12.4)	
Fibroscan not done	34 (48.6)	195 (39.8)	
Diabetes mellitus, no. (%)	5 (7.1)	37 (7.6)	0.882
Hypertension, no. (%)	17 (24.3)	107 (21.8)	0.638
Hyperlipidaemia, no. (%)	9 (12.9)	41 (8.4)	0.218
Cardiovascular disease, no. (%)	2 (2.9)	28 (5.7)	0.331
Laboratory results			
Creatinine, mean (SD), $\mu\text{mol/L}$	85.2 (19.5)	83.8 (18.1)	0.549
Albumin, mean (SD), g/L	43.7 (3.2)	44.6 (9.4)	0.428

Table 1. Baseline characteristics of HCV patients eligible for MM (n=560). (Cont'd)

	Minimal monitoring (n=70)	Standard of care (n=490)	P value
Bilirubin, mean (SD), $\mu\text{mol/L}$	11.6 (6.3)	12.9 (10.6)	0.317
ALT, mean (SD), U/L	66.2 (44.3)	59.7 (57.6)	0.365
Haemoglobin, mean (SD), g/dL	14.7 (1.7)	15.1 (7.0)	0.634
Platelet count, mean (SD), $\times 10^3/\mu\text{L}$	218.3 (60.1)	221.0 (68.2)	0.754
INR, mean (SD), sec	1.0 (0.1)	1.0 (0.1)	1
Baseline viral load, mean (SD), log IU/mL	6.0 (0.7)	6.0 (0.9)	1

ALT: alanine transaminase; HCV: hepatitis C virus; INR: international normalised ratio; MM: minimal monitoring; SD: standard deviation; SOC: standard of care

$P<0.001$), averting a total of 556 clinic visits in this cohort. Only 1 SAE (angioedema) occurred in the SOC arm, which resolved after cessation of DAA.

Our study is the first in Singapore to demonstrate the safety and efficacy of MM among HCV patients, including those with cirrhosis and multiple comorbidities. A previous trial by Dore et al.⁷ using simplified monitoring had excluded patients with cirrhosis and those for whom treatment compliance was a concern.⁷ However, our study confirmed MM's efficacy and safety in real-world scenarios with comparable SVR12 results, and SAE was uncommon with pan-genotypic DAA.

Although 92.1% of this group met the criteria for the MM strategy, only 12% utilised it, highlighting the potential for improving HCV care. The low uptake of the MM strategy was related to the lack of awareness of this strategy and safety concerns over DAA among physicians with less experience in DAA. Adoption of the MM strategy may reduce healthcare resource utilisation without compromising treatment outcomes. MM can be advantageous in low and middle-income countries (where 80% of chronic HCV patients reside) because pre-treatment genotype testing and on-treatment monitoring may not be feasible in resource-limited settings.^{7,8} Encouraging the use of MM can speed up HCV treatment expansion and facilitate treatment upscale for HCV elimination in Singapore. It is important to disseminate the real-world safety of the MM strategy and incorporate the MM strategy into

institutional HCV treatment protocol to provide confidence to physicians with less experience in DAA to adopt the MM strategy.

We acknowledge there were limitations in this study. Firstly, the introduction of the revised workflow to accommodate incarcerated patients for MM took place only in May 2020. Due to institutional safety requirements, incarcerated patients undergoing MM strategy were reviewed once by the prison medical team between DAA initiation and SVR12, which may affect the generalisability of our findings. Of note, none of the incarcerated patients undergoing MM was referred back to our institution during HCV treatment as a result of treatment-related adverse events. While there may be fewer opportunities to educate patients on treatment compliance and harm reduction, we found similar treatment compliance between MM and SOC groups.

In summary, MM with pan-genotypic DAA is an underutilised, efficacious and safe strategy in treatment-naïve HCV patients without prior decompensation. Physicians should consider the adoption of MM in the management of HCV, particularly in a resource-limited setting, to save healthcare resources and improve HCV treatment and elimination in Singapore.

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