Successful use of generic direct acting antiviral medications to treat hepatitis C—a New Zealand-wide study

Kristina Aluzaite, Margaret Fraser, Steve Johnson, Hannah Giles, Michael Schultz

ABSTRACT

AIMS: Direct acting antiviral (DAA) hepatitis C (HCV) medications are funded in New Zealand since 2016 for some and since 2019 for all genotypes. The purpose of this study was to review New Zealand-wide data of the use of generic HCV DAA medications imported through Tasmanian FixHepC Buyer’s Club and the associated side effect profiles.

METHODS: This is a retrospective data audit on the use of generic DAAs to treat HCV; outcomes from consecutive hepatitis C patients (naïve and pre-treated) treated with generic DAAs (sofosbuvir/ledipasvir, sofosbuvir/daclatasvir, sofosbuvir/ledipasvir, ribavirin) collected from all known sites that used Buyer’s club medications in eight New Zealand district health board regions were summarised. Demographic, disease characteristics, FibroScan and blood markers’ (platelets, ALT, GGT, AFP) data were collected.

RESULTS: Study sample was 81.8% New Zealand European, 64.8% male of median 56.0 (IQR: 48.0–60.0) years old. Three participants (4.5%) were HIV positive. 74.7% of the participants had signs of fibrosis (F1–F4); 40.5% had cirrhosis/scarring (F4). 61.7% of the patients were naïve to treatment. 42.0%, 40.1% and 12.0% received sofosbuvir/ledipasvir, sofosbuvir/daclatasvir, sofosbuvir/velpatasvir, respectively; 32.1% also received ribavirin. 80.2% of patients received treatment for 12 weeks. 95.1% (154/162) of the sample achieved sustained virological response at 12 weeks post-treatment, 2.5% relapsed, 1.2% were lost to follow-up. The main minor side effects included fatigue, headache, difficulty sleeping, experienced by 21.7%, 7.0%, 7.0%, respectively. An average total cost for medication and monitoring was 2,027 to 2,659 NZD (12 weeks), and 3,054 to 4,260 NZD (24 weeks) per patient.

CONCLUSIONS: Generic DAAs to treat hepatitis C are safe, efficient and a cheaper than branded medications option.

Hepatitis C is caused by an infection with blood-borne hepatitis C virus (HCV) that results in a chronic inflammatory process in the liver. Only a small proportion of the persons infected with HCV will develop symptomatic acute hepatitis, and while 18–34% of the patients will spontaneously clear the infection, the remainder will develop chronic disease that may lead to progressive fibrosis or cirrhosis.1

It is estimated that 71 (95% confidence interval 62.5–79.4) million people globally are living with chronic hepatitis C (HCV) infection (2015).2-3 Each year, over 399,000 deaths are attributable to hepatitis C-related liver disease, mostly due to complications related to liver cirrhosis or hepatocellular carcinoma.4 Hepatitis C is one of the leading indication for causes for liver transplantation worldwide.5 The exact prevalence of HCV infections in New Zealand is unknown, but it estimated that it is similar to that of Australia and is 1.28%, which equates to approximately 54,000 infected people.6
Due to the largely asymptomatic nature of chronic HCV infections, most cases remain undiagnosed, resulting in delayed treatment and liver damage; it is estimated that 30,000 New Zealanders have undiagnosed HCV infections. Prior to the introduction of funded DAA medications, treatment rates in New Zealand and elsewhere were low—only 1 in 10 of those diagnosed receive treatment globally and in New Zealand due to reasons such as limited healthcare infrastructure, lack of knowledge and/or inaccurate perceptions on patient and practitioner levels. Globally in 2015 there were more new HCV infections than patients who started treatment.

While HCV incidence has been stable, the HCV-associated disease burden is increasing due to aging population. Most of the advanced-liver disease, health costs and deaths could be avoided through the use of new generation direct acting antiviral (DAA) hepatitis C medications with reported cure rates above 95% and minimal side effect profile. This is an important improvement since the interferon-based therapies with poor medication tolerance, efficacy and substantial side effects.

In June 2016, New Zealand's Pharmaceutical Management Agency (PHARMAC) started to provide fully funded treatment for those with hepatitis C genotype 1, and for patients with genotypes 2 and 3 with advanced liver disease (Model for End-stage Liver Disease (MELD) >12). They received paritaprevir, ritonavir, ombitasvir and dasabuvir (Viekira Pak, AbbVie Ltd) or ledipasvir with sofosbuvir (Harvoni, Gilead Sciences, Inc.), respectively. In February 2019 then, glecaprevir and prebrentasvir (Maviret) was made available for all genotypes. During these two years, treatment of 44% of HCV patients in New Zealand was unfunded.

In some districts, monitoring of HCV treatment with self-purchased medications was expressly prohibited thus forcing some patients to seek prescriptions and treatment monitoring in the private sector. A number of studies, including the large observational REDEMPTION-1 trial (estimated enrolment—1,000 participants), show that the sustained virological response (SVR) rates using generic formulations of DAA HCV medications are above 90% and thus are comparable to the branded versions. The purpose of this study was to review New Zealand-wide data of the use of generic HCV DAA medications and the associated side effects profiles.

**Methods**

Data on the use of generic DAAs to treat hepatitis C infections were collected retrospectively in eight district health board (DHBs) regions across New Zealand: Southern DHB (SDHB), Auckland DHB (ADHB), Hutt Valley DHB (HuttDHB), Canterbury DHB (CDHB), Wairarapa DHB (WDHB), Counties Manukau DHB (CMDH), South Canterbury DHB (SCDHB) and Lakes DHB (LakesDHB) regions (Appendix Table 1). Data from all known adult participants, who received generic medication treatments obtained through the Buyers’ club between 1 January 2014 and 1 February 2018, were included. All New Zealand sites known to
treat patients with generic DAA medications were contacted for data and included public and private healthcare sectors.

The summarised data included demographic (age, sex, ethnicity), baseline disease characteristics (genotype, level of fibrosis, viral load, blood indicators of liver disease—platelets, ALT, GGT, AFP), type and duration of generic medications received, corresponding post-treatment blood indicators and viral loads. HIV co-infections were also recorded. Reported minor and major side effects were pooled.

SVR was considered when HCV RNA was <12 IU/ml 12 weeks after end of treatment. Relapse was defined as increase of HCV RNA at the end of the treatment within 24 weeks post-treatment. Data from the regions were combined and descriptive statistics were derived. Treatment efficacy was calculated by dividing patients who achieved SVR from the total number of patients, who started receiving treatment. Wilcoxon Rank sum test for paired samples was used to compare before and after treatment liver function tests’ and viral load levels.

All the participating sites used liver FibroScan to determine level of liver fibrosis, and the following METAVIR cut-off scores were assigned to describe the level of fibrosis: <7.1kPA was indicative of F0; <8.7kPA was indicative of F2; <9.5kPA was indicative of F3, and ≥12.5kPA suggested F4 (cirrhosis).

Liver function tests of alanine transaminase (ALT) and gamma-glutamyl transferase (GGT) levels were performed, and the following scores were considered as elevated: ALT >29 U/L for men and >22 U/L for women; GGT: >51 U/L for men and >33 U/L for women.

Results

We received data from nine sites in eight regions on 162 patients (49 SDHB, 33 ADHB, 24 HuttDHB, 24 CDHB and three from CDHB Hepatitis C Community Clinic, 11 WDHB, eight CMDHB, seven SCDHB, three Lakes DHB) treated with generic medications for their HCV infection. The study sample was 64.8% (105/162) male with median (25th–75th Q) age of 56.0 (48.0–60.0) years. 81.8%, 10.1% and 5.0%, identified with European, Asian or Māori ethnicities, respectively. At the time of the study, 368 New Zealand patients have accessed generic medications from FixHepC, which means we captured 44.0% of the population (information obtained through personal communication).

95.1% (154/162) of the treated patients achieved SVR12, 2.5% (4/162) relapsed (patients who relapsed had genotypes 1 (SOF/LDV), genotype 2 (SOF and SOF/DCV), genotype 3 (SOF/DCV)), 1.2% (2/162) were lost to follow-up and 1.2% (2/162) were still on treatment. 40.7% of patients had HCV genotype 1, 38.9% had genotype 3 and 14.2% had genotype 2. 40.5% scored F4 indicating of cirrhosis, followed by 25.3% F0 and 17.1% F1. 61.7% of the patients were HCV therapy naïve. Three patients were HIV positive.

42.0% (68/162) of the patients received sofosbuvir and ledipasvir, 41.4% (67/162) received sofosbuvir and daclatasvir, 12.3% (20/162) were treated with sofosbuvir and velpatasvir (Table 1). 32.1% (52/162) also received ribavirin.

The median (25th–75th Q) viral load at the start of the treatment was 1.1x10^6 IU/ml (3.4x10^5–3.0x10^6) (Appendix Figure 1), while platelets, ALT, GGT and AFP were 195.5 (145.5–247.5) U/L, 59.0 (39.3–108.5) U/L, 47.0 (25.0–100.8) U/L and 5.0 (3.7–10.0) U/L at the start, respectively. At the end of the treatment, platelets, ALT, GGT and AFP were 200.0 (150.5–260.0) U/L, 18.0 (14.0–27.0) U/L, 22.0 (16.0–42.5) U/L and 4.6 (2.9–5.4) U/L, respectively (Figures 1a–d). Viral load, ALT, AFP and GGT were significantly lower after treatment, with (p<0.007). There was no statistically significant difference in platelet counts (p=0.33). 69.3% (115/150) and 75.7% (112/148) of the subjects had normalised their ALT and GGT levels post-treatment, respectively.

Three out of the four patients who relapsed had FibroScan category F4, and genotypes 2 (2/4: received SOF or SOF/DCV) and 1 (1/4: received SOF/LDV). One patient scored F2 in FibroScan and had genotype 3 (1/4: received SOF/DCV). Only one of these patients (FibroScan category F4, genotype 2) experienced a minor side effect (headache).

Three incidents in two people were reported as major side effects. One patient reported myositis and worsening diabetic control (type 2 diabetes), while the second patient developed rapidly progressing
Table 1: Characteristics of the study sample by the generic treatment.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall n(%)</th>
<th>SOF/LDV† n(%)</th>
<th>SOF/DCV† n(%)</th>
<th>SOF/VEL† n(%)</th>
<th>SOF or SOF/Pinf† n(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of participants</td>
<td>162</td>
<td>68</td>
<td>67</td>
<td>20</td>
<td>7</td>
</tr>
<tr>
<td>Age, median (25th–75thQ)</td>
<td>56.0 (48.0–60.0)</td>
<td>56.5 (70.8–60.0)</td>
<td>52.0 (46.50–59.0)</td>
<td>55.0 (50.5–59.8)</td>
<td>59.0 (56.5–62.5)</td>
</tr>
<tr>
<td>Male</td>
<td>105 (64.8)</td>
<td>44 (64.7)</td>
<td>45 (67.2)</td>
<td>13 (65.0)</td>
<td>3 (42.9)</td>
</tr>
<tr>
<td>Female</td>
<td>57 (35.2)</td>
<td>24 (35.3)</td>
<td>22 (32.8)</td>
<td>7 (35.0)</td>
<td>4 (57.1)</td>
</tr>
<tr>
<td>Ethnicity, European</td>
<td>80.2%</td>
<td>83.8%</td>
<td>74.6%</td>
<td>80.0%</td>
<td>100.0%</td>
</tr>
<tr>
<td>Hepatitis C genotype</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1(combined)</td>
<td>66 (40.7)</td>
<td>58 (85.3)</td>
<td>6 (9.0)</td>
<td>1 (5.0)</td>
<td>1 (14.3)</td>
</tr>
<tr>
<td>1a</td>
<td>32 (19.8)</td>
<td>27 (39.7)</td>
<td>4 (6.0)</td>
<td>1 (5.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>1b</td>
<td>10 (6.2)</td>
<td>9 (13.2)</td>
<td>1 (1.5)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>2</td>
<td>23 (14.2)</td>
<td>2 (2.9)</td>
<td>14 (20.9)</td>
<td>3 (15.0)</td>
<td>4 (57.1)</td>
</tr>
<tr>
<td>3</td>
<td>63 (38.9)</td>
<td>4 (5.9)</td>
<td>44 (65.7)</td>
<td>13 (65.0)</td>
<td>2 (28.6)</td>
</tr>
<tr>
<td>4</td>
<td>3 (1.9)</td>
<td>1 (1.5)</td>
<td>2 (3.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>6</td>
<td>3 (1.9)</td>
<td>2 (2.9)</td>
<td>0 (0.0)</td>
<td>1 (5.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Multiple</td>
<td>4 (2.5)</td>
<td>1 (1.5)</td>
<td>1 (1.5)</td>
<td>2 (10.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>HIV, positive</td>
<td>3 (1.9)</td>
<td>1 (1.5)</td>
<td>2 (3.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Liver fibrosis (METAVIR)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>F0</td>
<td>40 (25.3)</td>
<td>24 (35.8)</td>
<td>9 (14.1)</td>
<td>4 (20.0)</td>
<td>3 (42.9)</td>
</tr>
<tr>
<td>F1</td>
<td>27 (17.1)</td>
<td>12 (17.9)</td>
<td>12 (18.8)</td>
<td>1 (5.0)</td>
<td>2 (28.6)</td>
</tr>
<tr>
<td>F2</td>
<td>11 (7.0)</td>
<td>4 (6.0)</td>
<td>6 (9.4)</td>
<td>1 (5.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>F3</td>
<td>16 (10.1)</td>
<td>6 (9.0)</td>
<td>10 (15.6)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>F4</td>
<td>64 (40.5)</td>
<td>21 (31.3)</td>
<td>27 (42.2)</td>
<td>14 (70.0)</td>
<td>2 (28.6)</td>
</tr>
<tr>
<td>Naïve to treatment</td>
<td>100 (61.7)</td>
<td>40 (58.8)</td>
<td>42 (62.7)</td>
<td>15 (75.0)</td>
<td>4 (57.1)</td>
</tr>
<tr>
<td>Treatment duration</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 weeks</td>
<td>1 (0.62)</td>
<td>0 (0.0)</td>
<td>1 (1.5)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>12 weeks</td>
<td>130 (80.2)</td>
<td>55 (80.9)</td>
<td>49 (73.1)</td>
<td>19 (95.0)</td>
<td>7 (100.0)</td>
</tr>
<tr>
<td>16 weeks</td>
<td>3 (1.9)</td>
<td>2 (2.9)</td>
<td>0 (0.0)</td>
<td>1 (5.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>24 weeks</td>
<td>28 (17.3)</td>
<td>11 (16.2)</td>
<td>17 (25.4)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Received Ribavirin</td>
<td>52 (32.1)</td>
<td>16 (23.5)</td>
<td>19 (28.4)</td>
<td>10 (50.0)</td>
<td>7 (100.0)</td>
</tr>
</tbody>
</table>

†No data for liver fibrosis for four patients.
‡SOF—Sofosbuvir; LDV—Ledipasvir; DCV—Daclatasvir; VEL—Velpatasvir; Pinf—Pegylated interferon.

multifocal HCC and decompensation that resulted in the patient's death; both of the patients still achieved SVR12. 63.7% of patients that received treatment did not report any side effects. The most common minor side effects were fatigue (21.7%), headache (7.0%), difficulty sleeping (7.0%), dry skin/rashes (7.0%), nausea (5.7%), poor mood and irritability (4.5%).

Discussion
We collected data from eight regions that collectively cover more than half of New Zealand's population (2013 census),24 and found 95.1% HCV treatment efficacy rates. This rate is comparable to other studies that investigated the use of generic DAAs to treat hepatitis C,25 as well as the use of branded...
medications.\textsuperscript{23} We captured approximately half of all the HCV patients treated through the FixHepC Buyers’ club, which renders this study representative of the population of interest.

Despite its high efficacy rates and easy treatment regimes, the HCV DAA medication uptake is very low, which to large extent is due to costs. Generic medications provide a safe, effective and affordable option both for patients outside funded treatment criteria and in countries where these medications are inaccessible.

The combined generic DAA medication and monitoring costs in our study were between 2,027 to 2,659 NZD (12 weeks), and 3,054 to 4,260 NZD (24 weeks)—a fraction of the cost of branded medications (55,000–113,000 USD).\textsuperscript{31} While low- and middle-income countries are guaranteed access to generic medications through compulsory licensing for medicines on the World Health Organization (WHO) Model List of Essential Medicines,\textsuperscript{18,32} 38% of chronic HCV patients worldwide (or 27 million people) are not eligible. Buyers’

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Change in blood markers before and after treatment, Wilcoxon Rank sum test for paired samples.}
\end{figure}

\begin{itemize}
\item a) Platelets, \(p=0.33\); b) ALT, \(p<0.001\); c) AFP, \(p=0.007\); d) GGT, \(p<0.001\).
\end{itemize}

\textsuperscript{*}due to visualisation purposes, high values ALT = 441, platelets = 1,660 and AFP = 545 were removed.
clubs, such as FixHepC, provide access to otherwise unaffordable medications in upper middle- and high-income countries. However, even the reduced cost could pose substantial challenges for the worse off. Furthermore, only 5.0% of the study sample were of Māori ethnicity—only a third of the general New Zealand population, possibly indicating that there were treatment access inequities. Further studies are required to clearly establish this.

The WHO is placing a major focus on the HCV disease burden and is calling for efforts to eliminate viral hepatitis as a public health threat by 2030 (reducing new infections by 90% and mortality by 65%) through the Global Health Sector Strategy on viral hepatitis 2016–2021. This was highlighted with the Global hepatitis report (2017) that set the baseline for tracking progress in implementing the strategy and released guidelines for care and treatment of those with HCV\(^\text{13}\) and access to treatment report (2018). Without publicly funded pangenotypic HCV medications or increased uptake of generic medications, New Zealand would not meet the WHO-set HCV elimination targets.

New Zealand's regulations permit a three months' worth of prescription medicines' import, however, restrictions exist with the prescribing clinician having to prove being able to take full responsibility for the quality and safety of the medication.\(^\text{35}\) The major concerns about the use of generic medications are their efficacy and safety. We identified few side effects with the majority of patients having none. The most common side effects were fatigue, headache, difficulty sleeping and dry skin. However, this data may be incomplete, as the appointment schedules and follow-up differed among treating sites. We also anticipate there being variation in the data recording.

This is a retrospective observational study with no control group, hence the collected data has inherent limitations in proving the efficacy of generic DAA HCV medications. However, an attempt was made to capture most cases of the use of generic medications, and all the sites known to treat hepatitis C patients were contacted. We captured 162 patients that is around half of the New Zealand patients known to have accessed FixHepC at the point of study since 2014.

New Zealand's PHARMAC has recognised the looming HCV-associated disease burden, and has now funded pangenotypic HCV treatment for all patients with chronic hepatitis C from early 2019. While it is anticipated that generic HCV medications will become less important in New Zealand, this data still relevant for other upper middle- and high-income countries with limited access to DAA hepatitis C medications.

In conclusion, this study provides a compelling case for clinical safety and efficacy of the generic DAA HCV medications to tackle one of outstanding global health challenges and achieve the WHO's goal to eliminate viral hepatitis as a public health threat by 2030 (also signed by New Zealand).
Appendix

Appendix Figure 1: Change in Viral Load (log10) at the baseline and 12 weeks after end of treatment ($p<0.001$). Purple data points—relapsed patients.

![Appendix Figure 1: Change in Viral Load (log10) at the baseline and 12 weeks after end of treatment ($p<0.001$). Purple data points—relapsed patients.](image)

Appendix Table 1: Hepatitis C patients treated with generic medications 1 January 2014–1 February 2018.

<table>
<thead>
<tr>
<th>District health board (DHB) regions</th>
<th>Number of patients treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Southern</td>
<td>49</td>
</tr>
<tr>
<td>Auckland</td>
<td>33</td>
</tr>
<tr>
<td>Hutt</td>
<td>24</td>
</tr>
<tr>
<td>Canterbury</td>
<td>27</td>
</tr>
<tr>
<td>Wairarapa</td>
<td>11</td>
</tr>
<tr>
<td>Counties Manukau</td>
<td>8</td>
</tr>
<tr>
<td>South Canterbury</td>
<td>7</td>
</tr>
<tr>
<td>Lakes</td>
<td>3</td>
</tr>
</tbody>
</table>
Competing interests:
Nil.

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We would like to thank Prof Ed Gane and Bridget Faire from Auckland DHB, Dr Jeffrey Wong from Hutt valley DHB, Jenny Bourke and Marilyn Brown from Canterbury District DHB, George Smith from Wairarapa DHB, Dr Stephen Gerred from Counties Manukau DHB, Dr Thomas Caspritz and Carly Bramley from South Canterbury DHB, Dr Richard Newbury and Lydia White from Lakes District DHB for compiling data. We thank Dr James Freeman and Greg Jefferys for providing statistics on the utilisation for FixHepC Buyers’ club in New Zealand.

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REFERENCES:
8. Dore GJ, Ward J, Thrusz M. Hepatitis C disease burden and strategies to manage the burden (Guest Editors Mark Thrusz, Gregory Dore and John Ward).


30. 2013 Census district health board tables.


