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Original Article

Hematological and Biochemical Changes after Anti-Hepatitis C Virus Therapy in Older Patients

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SUMMARY

Background: Hepatitis C virus (HCV) infection is a global problem, and older patients are more likely to develop advanced liver disease. Direct-acting antiviral treatments (DAA) have revolutionized the paradigm of HCV treatment and made its elimination possible. However, hematological and biochemical changes have rarely been discussed.
Methods: This was a retrospective observational study of enrolled patients who received DAA for chronic HCV between Aug 2018 and Mar 2020. Patients were divided into two groups: younger < 65 years and older ≥ 65 years. The HCV genotype, changes in biochemistry and hematologic data before and after treatment, and sustained virologic response at 12 weeks after cessation of drug administration were recorded.
Results: Of the 226 enrolled patients, 130 (57.5%) belonged to the younger group and 96 (42.5%) to the older group. Most patients had HCV genotype 2 infections (54.4%), and older patients tended to have genotype 2 infections (70.7% vs. 42.3%). The older patients had significantly lower hemoglobin, platelet, albumin, and BUN levels initially. After treatment, the platelet count and BUN levels significantly improved in older patients. Older patients had higher fibrosis-4 (FIB-4) scores than younger patients before and after treatment. After treatment, the FIB-4 score in the older group showed a significant change (3.90 vs. 2.67; p = 0.001), but the younger group did not (1.97 vs. 1.75; p = 0.05).
Conclusion: Older patients tended to have genotype 2 infections. After DAA treatment, the improvements in platelet count and albumin level were better in older patients than in younger patients. Improvement in FIB-4 was also significant in the older population.

1. Introduction

Hepatitis C virus (HCV) infection is a global problem with a global prevalence of 2.5%. Older patients with chronic HCV are more likely to develop advanced liver diseases, including cirrhosis, hepatocellular carcinoma, and related complications, than younger ones.[1–4] Direct-acting antiviral (DAA) treatments have revolutionized the paradigm of hepatitis C treatment and made its elimination possible due to its high efficacy.[5] Glecaprevir and pibrentasvir (G/P, Maviret)", a pangenotypic DAA, demonstrates high sustained virologic response (SVR) rates at 12 weeks and good safety profile even in patients with comorbidities like decompensated cirrhosis, prior treatment failures, and chronic kidney disease.[4] However, patients above 65 years old were underrepresented in the original phase 3 licensing studies for most DAA regimens.[6] Besides, older patients tend to have multiple comorbidities and co-medications, making possible drug-drug interactions or complications a concern when receiving DAA.[5] In addition, most previous studies focus on the efficacy of the DAA and ignore the hematological and biochemical changes after treatment, especially in older patients. This study aimed to assess the hematological and biochemical changes after anti-HCV therapy in older patients.

2. Patients and methods

2.1. Patients

We retrospectively reviewed the medical records of patients who received G/P for chronic HCV infection between August 2018 and March 2020 at MacKay Memorial Hospital, a tertiary medical center in Taiwan. Patients were divided into two groups: younger (< 65 years) and elderly (≥ 65 years). The patients' sex, HCV viral load, and comorbidities were recorded. Treatment efficacy was defined as the rate of sustained virologic response 12 weeks after the cessation of drug administration. Blood samples were collected before treatment and 12 weeks after the cessation of drug administration to measure changes in aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin, total bilirubin, blood urea nitrogen (BUN), serum creatinine, and complete blood counts.

This retrospective study was conducted in accordance with the principles of the Declaration of Helsinki and approved by the Institutional Review Board of MacKay Memorial Hospital (21MMHIS 198e).

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2.2. The fibrosis-4 index

The fibrosis-4 (FIB-4) index is a scoring system used to assess liver fibrosis. The variables used were age, AST level, ALT level, and platelet (PLT) count, and the formula was as follows: (age [y] × AST [U/L]) / ((PLT [10^9/L]) / (ALT [U/L])$^{1/2}$). The area under the receiver operating characteristic (AUROC) of the index was 0.765 for differentiation between Ishak stage 0–3 and 4–6.[7,8] FIB-4 was also calculated before treatment and at SVR12. As age is one of the variables of FIB-4, we only discussed the change in FIB-4 after treatment between the two groups. We did not discuss the initial and final FIB-4 scores between the groups.

2.3. Statistical analysis

All statistical analyses were conducted using Stata software, version 12.0 (StataCorp LP, College Station, Texas). Continuous variables were expressed as medians and standard deviations. Categorical variables were expressed as numbers and percentages. Comparisons between groups were conducted using the Mann-Whitney U-test for continuous and ordinal variables and the χ^2 test for categorical variables. A p-value < 0.05 was considered significant.

3. Results

3.1. Patients

There were 237 patients with chronic HCV infection enrolled in this study. There were 10 patients, included 6 (4.4%) younger patients and 4 (4.0%) elderly patients (p = 0.03) lost to follow-up before completing the glecaprevir and pibrentasvir (G/P) treatment, and one died due to pneumonia. Therefore, they were excluded from the analysis.

The demographic, disease, and clinical characteristics of the 226 enrolled patients at baseline are presented in Table 1. In total, 130 (57.5%) and 96 (42.5%) patients were included in the younger and older groups, respectively. Overall, 5.3%, 11.1%, 29.6%, and 13.3% of patients had hepatic cellular carcinoma, diabetes mellitus (DM), chronic kidney disease, and hypertension, respectively. The older patients had a high prevalence of these comorbidities with statistical significance compare with younger ones.

The HCV viral load was nearly equal between both groups (younger vs. elderly: 7.65 ± 6.89 log IU/mL vs. 6.69 ± 7.85 log IU/mL; p = 0.99). The HBV co-infection rate was also similar in both groups (younger vs. older: 3.1% vs. 4.2%; p = 0.66). Among the 226 patients who completed the treatment, two failed to achieve SVR12 (1.5%), and both were in the younger group (Table 1).

One hundred and twenty-three patients (54.4%) had HCV genotype 2 infections, 14 (6.2%) had genotype 1a infections, 55 (24.3%) had genotype 1b infections, 12 (5.3%) had genotype 3 infections, 16 (7.1%) had genotype 6 infections, and 6 (2.7%) had mixed genotype infections. Compared with younger patients, older patients tended to have genotype 2 infections (70.7% vs. 42.3%, p < 0.01) (Figure 1).

Table 1
Demographic characteristics of the study participants.

	Younger (n = 130)	Older (n = 96)	All patients (n = 226)	p-value
Age	51.5 ± 10.3	73.5 ± 6.1	60.88 ± 14.0	< 0.01
Gender (male)	67 (51.5%)	42 (43.8%)	109 (48.2%)	0.25
HCC history	3 (2.3%)	9 (9.4%)	12 (5.3%)	0.019
Diabetes mellitus	9 (6.9%)	16 (16.7%)	25 (11.1%)	0.02
Chronic kidney disease*	24 (18.5%)	43 (44.8%)	67 (29.6%)	< 0.01
Hypertension	4 (3.1%)	26 (27.1%)	30 (13.3%)	< 0.01
Treatment failure	2 (1.5%)	0 (0%)	2 (0.8%)	0.22
HBsAg (+)	4 (3.1%)	4 (4.2%)	8 (3.5%)	0.66
HCV RNA (log IU/mL)	7.65 ± 6.89	6.69 ± 7.85	7.65 ± 6.87	0.99
FIB-4 index**				
Before treatment	1.97 ± 1.42	3.90 ± 3.73	2.79 ± 2.82	< 0.001
After treatment	1.75 ± 1.25	2.67 ± 1.43	2.14 ± 1.71	0.004

* Chronic kidney disease: GFR < 60.
** FIB-4 index: the fibrosis-4 index, a scoring system to estimate the fibrosis of the liver.

3.2. Hematological changes

In the Table 2, it shows the laboratory data obtained before and after the G/P treatment. Before treatment, the blood test results showed significant differences in hemoglobin and platelet counts between the two groups (Hemoglobin: younger vs. older 13.58 ± 2.26 vs. 12.58 ± 1.76; p < 0.01) (Platelet: younger vs. elderly: 202.6 ± 71.2 × 103 vs. 166.8 ± 58.6 × 103; p < 0.01). After treatment, the older group still had lower hemoglobin and platelet counts than the younger group. However, the condition of low platelet count was significantly improved in the older group (p < 0.01) but not in the younger group.

3.3. Biochemical changes

The older patient had more comorbidity, and potential concomitant drug-drug interactions during HCV treatment, so the biochemical changes must be assessed. Table 2 also shows the biochemical changes before and after 12 weeks of G/P treatment. After treatment, significant improvements in the albumin, AST, and ALT levels were observed in both groups. Initially, low albumin (younger vs. older: 4.4 ± 0.4 vs. 4.1 ± 0.4; p < 0.01) and BUN (younger vs. older: 17.4 ± 14.3 vs. 23.6 ± 17.4; p < 0.01) levels were found in the older patients than younger patients. The BUN and creatinine levels were stable before and after the treatment in both groups, with mild impairment of the BUN level in the older patients (23.6 ± 17.4 change to 25.90 ± 19.3, p = 0.02).

3.4. The FIB-4 index

As shown in Table 1, before and after treatment, the older patients had a higher FIB-4 score than the younger patients. As age is one of the variables of FIB-4, we discussed the change in FIB-4 scores after treatment between the two groups. As shown in Figure 2, after treatment, the FIB-4 score in the older group showed a significant change (3.90 vs. 2.67; p = 0.001) but not in the younger group (1.97 vs. 1.75; p = 0.05).

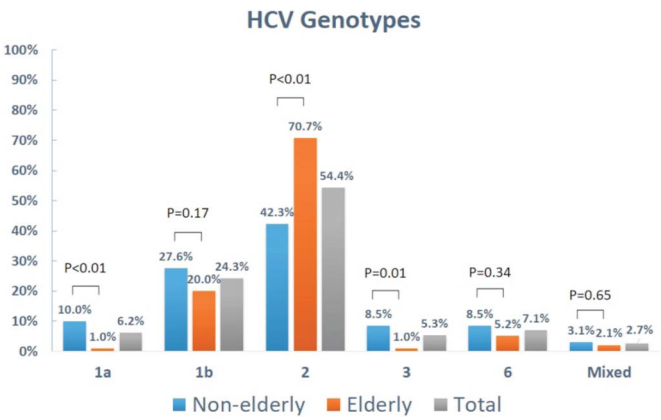

Figure 1. The distribution of the hepatitis C virus (HCV) genotypes.

Table 2
Hematological and biochemical changes before and after 12 weeks of treatment.

	Younger (n = 130)	Older (n = 96)	All patients (n = 226)	p-value
Hematological changes				
Hemoglobin				
Before	13.6 ± 2.3	12.6 ± 1.8	13.2 ± 2.1	< 0.01
After	13.6 ± 2.0	12.6 ± 2.0	13.2 ± 2.0	< 0.01
p-value	0.84	0.71	0.70	
WBC				
Before	5666.2 ± 1802.3	5421.9 ± 1732.1	5562.4 ± 1773.0	0.31
After	6191.5 ± 2073.0	5778.1 ± 1917.9	6015.9 ± 2014.7	0.18
p-value	< 0.01	0.07	< 0.01	
Platelet				
Before	$203 \pm 71 \times 10^3$	$167 \pm 59 \times 10^3$	$187 \pm 68 \times 10^3$	< 0.01
After	$213 \pm 93 \times 10^3$	$181 \pm 58 \times 10^3$	$200 \pm 81 \times 10^3$	< 0.01
p-value	0.12	< 0.01	< 0.01	
Biochemical changes				
Albumin				
Before	4.4 ± 0.4	4.1 ± 0.4	4.3 ± 0.4	< 0.01
After	4.5 ± 0.6	4.3 ± 0.4	4.4 ± 0.5	0.04
p-value	0.03	< 0.01	< 0.01	
Total bilirubin				
Before	0.76 ± 0.41	0.68 ± 0.22	0.73 ± 0.34	0.06
After	0.84 ± 1.35	0.69 ± 0.27	0.78 ± 1.04	0.29
p-value	0.51	0.50	0.44	
GOT				
Before	51.6 ± 38.2	53.7 ± 35.1	52.5 ± 36.9	0.67
After	26.6 ± 19.3	24.9 ± 9.5	25.9 ± 15.8	0.45
p-value	< 0.01	< 0.01	< 0.01	
GPT				
Before	67.0 ± 60.1	57.2 ± 48.1	62.8 ± 55.4	0.19
After	23.2 ± 20.6	19.0 ± 10.0	21.4 ± 17.1	0.07
p-value	< 0.01	< 0.01	< 0.01	
Creatinine				
Before	1.72 ± 0.25	2.24 ± 0.28	1.94 ± 0.19	0.166
After	1.75 ± 0.23	2.23 ± 0.29	1.95 ± 0.18	0.179
p-value	0.86	0.21	0.44	
BUN				
Before	17.4 ± 14.3	23.6 ± 17.4	20.1 ± 16.0	< 0.01
After	17.6 ± 12.5	25.90 ± 19.3	21.2 ± 16.3	< 0.01
p-value	0.72	0.02	0.05	

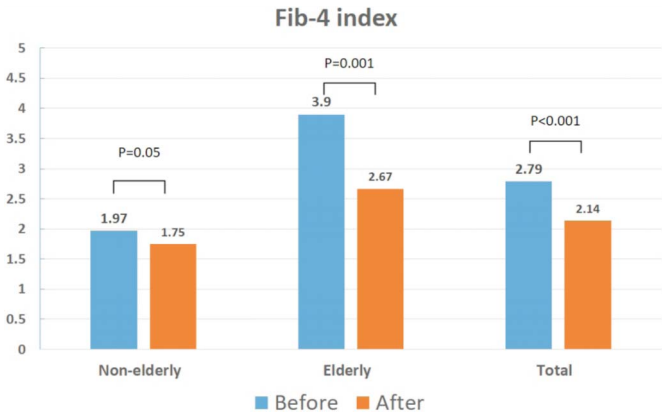

Figure 2. The fibrosis scores of the liver (FIB-4) before and after treatment.

4. Discussion

Older patients have an urgent need for HCV treatment since the older population remains at high risk for HCC and end-stage liver diseases even after eradication of the virus.[3] Before initiating HCV treatment, HCV genotype, liver fibrosis status, comorbidity (such as DM, renal disease, hypertension…etc.), and potential concomitant drug-drug interactions must be assessed.[1] The findings of this study showed that older patients had more comorbidities, such as hepatocellular carcinoma (9.4%), DM (16.7%), chronic kidney disease (44.8%), and hypertension (27.1%). In previous study, HCV-infected patients concerning the prevalence of DM and insulin resistance.[9] HCV-related autoimmune process may be one of the reason. In addition, a study in the United States also showed type 2 diabetes occurs more often in older persons with HCV infection.[10] In a real-world retrospective study of HCV management in geriatric patients with HCV infection in Taiwan also showed high prevalence rate (18.9%) of DM.[11]

The predominant HCV genotype in this study was type 2 (54.4%), followed by type 1 (30.5%, 1a + 1b). The distribution of the HCV genotypes was similar to that reported in a recent nationwide registry study in Taiwan. Most of the registry patients had HCV genotype 2 infections (45%), and 40.8% had genotype 1 infections.[12] In our study, we also found that older patients had more genotype 2 infections than younger patients (70.7% vs. 42.3%, $p < 0.01$).

In our study, both groups showed a significant decrease in AST and ALT levels after G/P treatment. There was a significant increase in platelet count in the older group from $167 \pm 59 \times 10^3/\mu l$ to $181 \pm 58 \times 10^3/\mu l$ but not in the younger group. Mechanisms of HCV-related thrombocytopenia and its improvement after viral elimination are complex. The causes of HCV-related thrombocytopenia include splenomegaly, autoimmune response (platelet-associated IgG), inadequate production of TPO due to liver fibrosis, and myelosuppression of the HCV virus. In a study of 4922 patients, Chen et al. identified several factors that predicted significant platelet improvement in patients with HCV after receiving DAA treatment, including younger age, presence of DM, and lower baseline platelet counts; however, the rapid increase in platelet count after HCV elimination was

not related to improvement in liver fibrosis.[13] Our study showed that older patients had good attenuation of thrombocytopenia after DAA treatment compared to younger patients, but the influence of liver fibrosis need further evaluation in the future.

In this study, older patient also had lower hemoglobin level before and after treatment of HCV. However, there was no significant change after treatment in both groups. Anemia was found more frequency in older HCV patients due to multiple comorbidities. In our study, there was no significant change of hemoglobin after HCV treatment. This may also imply no direct relationship between HCV infection and anemia.

Studies by Tahtasakal et al. and Ogasawara et al. suggested positive correlations between FIB-4 scores and the histologic severity of liver fibrosis in patients with HCV receiving DAA treatment.[14,15] Two Japanese retrospective studies also support our findings regarding AST, ALT, and FIB-4. Kinoshita et al. found that patients aged ≥ 75 years and < 75 years had significant reductions in FIB-4 scores after SVR12. Nakajima et al. also revealed that patients of different age groups (< 65 years, 65–75 years, and > 75 years) with an initial FIB-4 > 1.45 all showed significant reductions in AST, ALT, and FIB-4 scores after SVR12.[4,16] Therefore, in our study, the significantly decreased AST, ALT, and FIB-4 levels in both age groups at SVR12 may indicate that the lower initial platelet counts and higher prevalence of DM in the older group may be the causes of the significant increase in platelet counts after treatment. High prevalence of DM in elderly patients with HCV infection was also found in other studies.[17] The study by Nakajima et al. revealed that albumin levels improved 1 year after successful HCV eradication regardless of patient age, and it was related to the recovery of the liver reserve.[16] In our study, the older patients had lower pretreatment albumin levels, which is a risk factor for poor treatment outcomes. However, at SVR12, the older group showed significant improvement in albumin levels.

Glecaprevir/pibrentasvir have been found to be safe and effective in patients with chronic kidney disease (CKD) and end-stage renal disease.[18,19] Villani et al. found that DAA can improve renal function in patients with an estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m^2 or those aged ≥ 65.[20] The older patients in our study had a higher prevalence of CKD with eGFR < 60 ml/min/1.73 m^2 than the younger ones. There was no significant improvement in renal function after DAA treatment; however, renal function remained stable. Our study was limited by its small sample size and lack of detailed and uniform documentation of liver fibrosis (for example, biopsy or elastography).

There were limitations of the study. First, this was a retrospective study with a limited follow-up duration of 3 months, which may be insufficient to demonstrate the benefits of antiviral therapy. Second, we only enrolled patients with G/P only, and the effects of different anti-viral drugs for HCV elimination could not be adequately discussed here. Third, we only discussed some risks or findings, and further investigation must be discussed in the future.

In conclusion, older patients with HCV infection (> 65 years) had more severe liver fibrosis (high FIB-4 score), poorer renal function, and more comorbidities than younger patients. However, with glecaprevir/pibrentasvir, the older patients had similar SVR12 rates, attenuation of liver inflammation, and fibrosis as younger patients. Liver function and platelet count also improved. The patients' renal functions remained unchanged.

References

1. Mohammed Abdul MK, Snyder HS, Chunduru M, Lee SMK, Satapathy SK. Hepatitis C virus in the elderly in the direct-acting antiviral era: From diagnosis to cure. *Curr Treat Options Infect Dis.* 2020;12:296–309. doi:10.1007/s40506-020-00231-8
2. Thein HH, Yi Q, Dore GJ, Krahn MD. Estimation of stage-specific fibrosis progression rates in chronic hepatitis C virus infection: A meta-analysis and meta-regression. *Hepatology.* 2008;48:418–431. doi:10.1002/hep.22375
3. Huang CF, Yu ML. Treating hepatitis C in the elderly: Pharmacotherapeutic considerations and developments. *Expert Opin Pharmacother.* 2017;18:1867–1874. doi:10.1080/14656566.2017.1400010
4. Kinoshita A, Koike K, Mizuno Y, et al. Efficacy and safety of glecaprevir/pibrentasvir in patients with hepatitis C virus infection aged ≥ 75 years. *Geriatr Gerontol Int.* 2020;20:578–583. doi:10.1111/ggi.13919
5. Yu ML, Chen PJ, Dai CY, et al. 2020 Taiwan consensus statement on the management of hepatitis C: Part (I) general population. *J Formos Med Assoc.* 2020;119:1019–1040. doi:10.1016/j.jfma.2020.04.003
6. Parmar P, Shafran SD, Borgia SM, Doucette K, Cooper CL. Hepatitis C direct-acting antiviral outcomes in patients 75 years and older. *JGH Open.* 2020;5:253–257. doi:10.1002/jgh3.12480
7. Sterling RK, Lissen E, Clumeck N, et al. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. *Hepatology.* 2006;43:1317–1325. doi:10.1002/hep.21178
8. Kurosaki M, Izumi N. External validation of FIB-4: Diagnostic accuracy is limited in elderly populations. *Hepatology.* 2008;47:352–353. doi:10.1002/hep.21978
9. Desbois AC, Cacoub P. Diabetes mellitus, insulin resistance and hepatitis C virus infection: A contemporary review. *World J Gastroenterol.* 2017;23:1697–1711. doi:10.3748/wjg.v23.i9.1697
10. Mehta SH, Brancati FL, Sulkowski MS, Strathdee SA, Szklo M, Thomas DL. Prevalence of type 2 diabetes mellitus among persons with hepatitis C virus infection in the United States. *Ann Intern Med.* 2000;133:592–599. doi:10.7326/0003-4819-133-8-200010170-00009
11. Yen HH, Su PY, Liu IL, et al. Direct-acting antiviral treatment for hepatitis C virus in geriatric patients: A real-world retrospective comparison between early and late elderly patients. *PeerJ.* 2021;9:e10944. doi:10.7717/peerj.10944
12. Cheng PN, Mo LR, Chen CT, et al. Sofosbuvir/velpatasvir for hepatitis C virus infection: Real-world effectiveness and safety from a nationwide registry in Taiwan. *Infect Dis Ther.* 2022;11:485–500. doi:10.1007/s40121-021-00576-7
13. Chen YC, Chang TS, Chen CH, et al. Factors associated with significant platelet count improvement in thrombocytopenic chronic hepatitis C patients receiving direct-acting antivirals. *Viruses.* 2022;14:333. doi:10.3390/v14020333
14. Tahtasakal CA, Oncul A, Sevgi DY, Demirbas D, Gunduz A, Dokmetas I. Fibrosis scores that can be used in follow-up of after direct-acting antiviral treatment: Apri, FIB-4, king score and GUCI. *Eur J Gastroenterol Hepatol.* 2022;34:308–315. doi:10.1097/MEG.0000000000002204
15. Ogasawara N, Kobayashi M, Akuta N, et al. Serial changes in liver stiffness and controlled attenuation parameter following direct-acting antiviral therapy against hepatitis C virus genotype 1b. *J Med Virol.* 2018;90:313–319. doi:10.1002/jmv.24950
16. Nakajima T, Karino Y, Hige S, et al. Aging impairs fibrosis-4 index after sustained virologic response by direct-acting antivirals in chronic hepatitis C infection. *Ann Hepatol.* 2022;27:100566. doi:10.1016/j.aohep.2021.100566
17. Ndako JA, Owolabi AO, Olisa JA, et al. Studies on the prevalence of hepatitis C virus infection in diabetic patients attending a tertiary health-care facility south-west Nigeria. *BMC Infect Dis.* 2020;20:664. doi:10.1186/s12879-020-05388-7
18. Atsukawa M, Kondo C, Kawano T, et al. Development of interferon-free, direct-acting antivirals treatment for Japanese patients with chronic hepatitis C infection and chronic kidney disease. *J Nippon Med Sch.* 2021;88:163–170. doi:10.1272/jnms.JNMS.2021_88-316
19. Gane E, Lawitz E, Pugatch D, et al. Glecaprevir and pibrentasvir in patients with HCV and severe renal impairment. *N Engl J Med.* 2017;377:1448–1455. doi:10.1056/NEJMoa1704053
20. Villani R, Romano AD, Sangineto M, Serviddio G. Direct-acting antivirals improve kidney function in diabetic patients with HCV infection and chronic kidney disease. *Intern Emerg Med.* 2021;16:1239–1245. doi:10.1007/s11739-020-02628-1