

C型肝炎ウイルス排除後通院継続状況と再感染の有無、およびHCV感染誤認についての調査

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研究要旨

C型肝炎ウイルス排除（SVR 症例）においては、SVR 後の肝細胞癌（HCC）発生のリスクを鑑みわが国ではほぼ全例に定期的な通院・HCC サーベイランスの継続が推奨されている。大垣市民病院において、SVR 達成後の定期通院継続率を調査した。この結果、SVR 後通院継続率は持続的に低下し、SVR 後 5 年で 76.6%・10 年で 62.4%・15 年で 48.8%・20 年で 35.3%となった。通院継続率は治療前の肝線維化の程度で差はみられず、SVR 後 5 年目の通院継続率は IFN-SVR で 88.6%・DAA-SVR で 57.5%と後者で有意に低かった ($p < 0.0001$)。SVR 後 5 年目の通院継続率は genotype 1b 74.4%・2a 82.8%・2b 63.1%と genotype 2b 症例の通院継続率は有意に低かった (1b vs 2b : $p = 0.0015$ ・2a vs 2b : $p < 0.0001$)。多変量解析では SVR 後 drop-out に関与する因子は DAA (HR 4.473・95% CI 3.414-5.889) と genotype 2b (HR 1.169・95% CI 0.992-1.376)であった。一方通院継続例において、血中 HCV RNA を計 23187 回測定したが陽転した例はなく、わが国では drop out 症例以外で SVR 後 HCV 再感染が起こることはないと考えられた。また同時に今後は drop out 症例への対策が必要であると考えられた。逆に多施設の調査において SVR 症例において、HCV が排除されているにもかかわらず抗体陽性が持続していることから「C型肝炎である」と誤認された症例が 2246 例中 197 例 (8.8%) に認められ、この半数以上が指摘された際に自分の C型肝炎ウイルス感染の治癒について不安を感じていた。このことから、肝臓専門医以外の一般の医療現場において、現状で多くの C型肝炎抗体陽性者が HCV 感染を脱しており、ウイルスフリーであることを敷衍していく必要性が示唆された。

共同研究者

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このことを通院継続令において検証する。一方で、SVR を達成し HCV 排除されているにもかかわらず、HCV 抗体陽性なことから一般医療で持続感染していると誤解される例が少なくない。今回これらの実態についても他施設共同研究で把握を目指す。

A. 研究目的

C型慢性肝炎症例においては、直接作動型抗ウイルス薬 (DAAs) の臨床使用により、ほぼ全例で C型肝炎ウイルス (HCV) の排除 (SVR) が可能となったが、SVR 後に発生する肝細胞癌 (HCC) のリスクを鑑みてわが国では SVR 後症例は基本的に定期通院を継続し、HCC のサーベイランスを行うことが推奨されている。しかしながら、推奨にもかかわらず通院を中断し drop out する症例が少なくない。これらの実態を調査するとともに、drop out 症例の特徴を把握する。また、わが国においては一旦 SVR となった症例における HCV 再感染は少ないと考えられているが、

B. 研究方法

① SVR 後通院継続・drop out の実態

大垣市民病院で SVR を達成した HCC 既往のない 1329 例 (IFN による SVR 720 例・DAA による SVR 609 例) を対象とし、SVR 後の通院実態を調査した。また通院継続率を持続感染時の年齢・肝線維化の程度・治療方法・HCV genotype 別に比較した。

② 通院継続例における SVR 後 HCV 再感染の有無

大垣市民病院で SVR 達成後、通院継続をしていた上記症例において、SVR24 達成後に測定した血中 HCV RNA の結果を全て調査した。

③ SVR 達成後の HCV 感染誤解の頻度と詳細

多施設共同研究（大垣市民病院・三豊総合病院・旭中央病院・北里大学病院・聖マリアンナ医科大学病院・日本医科大学病院・済生会新潟病院・キッコーマン総合病院・愛媛県立中央病院・手稲溪仁会病院・慈恵医科大学病院・横浜市立大学市民医療センター・新松戸中央総合病院・大阪済生会吹田病院）より、各施設の SVR 後外来通院継続患者に対して「HCV 感染がある」と誤認指摘された症例の頻度、状況など詳細を調査した。

C. 研究結果

① SVR 後通院継続・drop out の実態

大垣市民病院における SVR 後の外来通院継続率は、SVR 後 5 年で 76.6%・10 年で 62.4%・15 年で 48.8%・20 年で 35.3%であった（図 1）。これを年齢別にみると、高齢者で継続率が低い傾向にあったが著大な差は認められなかった。また SVR 前の肝線維化で比較すると、通院継続率は肝線維化の重度であった症例と軽度であった症例で差はなく、HCC 発生のリスクが高いとされる線維化進行例でも軽度線維化例と同程度に drop out していることがわかった（図 2）。一方、治療法別にみると、インターフェロン（IFN）治療で SVR を達成した症例に対して経口 HCV 薬（DAA）で SVR を達成した症例において明らかに通院継続率が低く（図 3）、drop out 率が高く、注意が必要であると考えられた。また genotype 別に通院継続率を見ると、genotype 2b 型に感染していた症例で有意に通院継続率が低かった（図 4）。わが国において genotype 2b 感染は比較的若年者に多く、医療や輸血以外の感染経路の可能性が高い症例が多いと言われている。これら症例の drop out 率が高いことは SVR 後の HCV 再感染のリスクも含め十分な留意が必要であると考えられる。

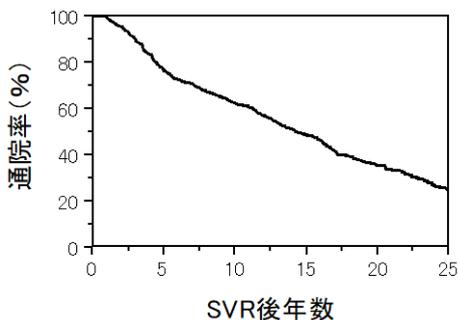


図1: 全症例のSVR後通院継続率(n = 1329)

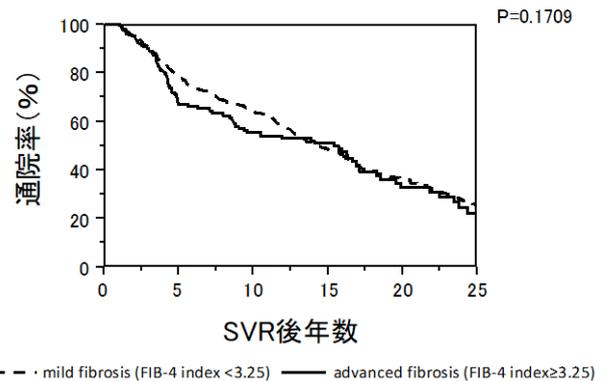


図2: SVR時の肝線維化別のSVR後通院継続率

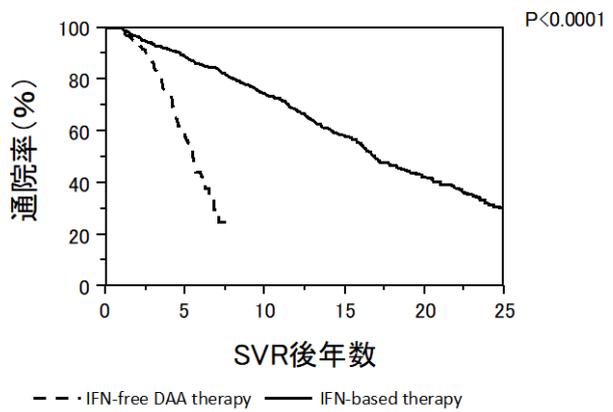


図3: SVRを達成した治療法別のSVR後通院継続率

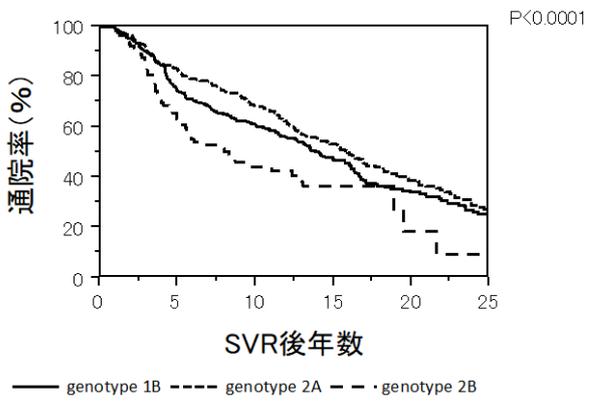


図4: HCV genotype別のSVR後通院継続率

② 通院継続例における SVR 後 HCV 再感染の有無

大垣市民病院で SVR を達成した HCC 既往のない 1329 例において、SVR 確定後に血中 HCV RNA をのべ 23187 回測定したが、HCV の再陽転化を認めた症例は皆無であった（表 1）。このことからわが国においては、少なくとも SVR 後 drop out していない症例においては HCV の再感染はないと考えられた。一方で、上述のごとく drop out 症例には再感染リスクの

高い症例が含まれている可能性がありこれら症例の検討が今後望まれる。

表1:SVR症例の患者背景とSVR後のHCV RNA

	IFN-based therapy (N= 720)	IFN-free therapy (N= 609)
Age (years)*	55.8 (46.1-62.4)	69.9 (62.3-81.1)
Gender (male/ female)	405 (56.3) / 315 (43.8)	257 (42.2) / 352 (57.8)
HIV coinfection	0	0
Drug user	0	0
Duration after SVR		
≤ 5 years	96 (13.3)	494 (81.1)
5< and ≤ 10 years	190 (26.4)	115 (18.9)
10< and ≤ 15 years	208 (28.9)	0
15< and ≤ 20 years	108 (15.0)	0
20< and ≤ 25 years	52 (7.2)	0
>25 years	66 (9.2)	0
Number of visits	24.3 (15.0-33.2)	8.3 (6.9-9.6)
Patients with current visit	341 (47.4)	407 (66.8)
Positive HCV RNA after SVR	0	0

*SVR時の年齢

③ SVR 達成後の HCV 感染誤解の頻度と詳細

SVR 達成後外来通院継続症例において、HCV 排除後にもかかわらず HCV 感染例と誤認された症例の頻度を検討した。全例 SVR 後も HCV RNA の陰性は確認されていた。全体として、2246 例中 197 例 (8.8%) で HCV 抗体陽性を根拠として HCV 感染していると誤認されていた (図 5)。このうち 105 例 (53.3%) で指摘された際に自分の C 型肝炎ウイルス感染の治癒について自信をなくし不安を感じていた (図 6)。誤認された状況は診療所が 55.3% と最も多く、総合病院 22.3%、検診 16.2% の順であった (図 7)。

C型肝炎治療後に「C型肝炎に感染している」と言われたことがありますか？

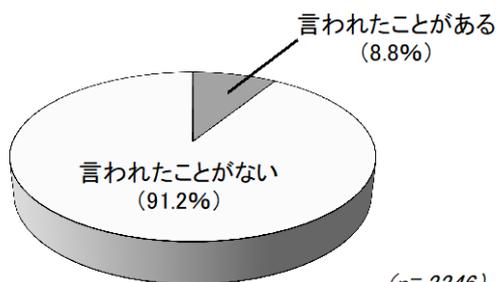


図5

その時にあなたは不安になりましたか？

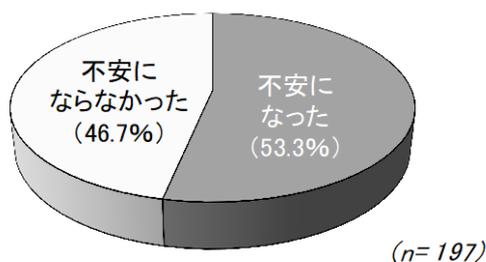


図6

HCV感染を誤認された状況

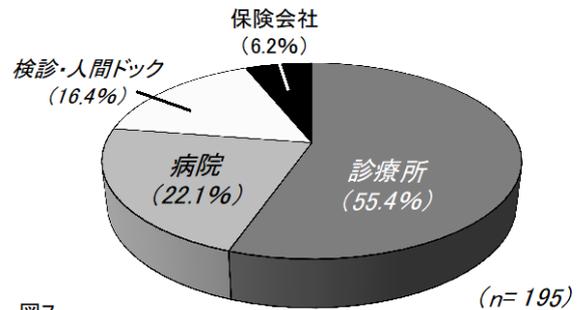


図7

D. 結論

今回の検討から SVR 後の診療状況が明らかとなった。SVR 後の HCC 発生のリスクは肝臓専門医の間ではよく認識されているものの、予想以上に SVR 後通院 drop out している症例が多いことが判明した。Drop out は肝線維化の程度、すなわち SVR 後 HCC の発生リスクによらないことが判明した。今後 SVR 後発癌リスクの明確化・層別化と患者に対する SVR 後通院の重要性の再教育が必要である。一方、SVR 後 HCV 再感染はわが国では非常に稀であることが確認された。一方で、肝臓専門医には常識である SVR 症例、HCV 抗体陽性である HCV 陰性例の急激な増加は一般医療においては十分に認識されておらず、今後これら知識の敷衍が必要であると考えられた。

E. 健康危険情報

特記すべきことなし。

F. 研究発表

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