# Analysis of the response to interferon-based therapy for hepatitis C virus infection in patients with inherited bleeding disorders during 1992 – 2012

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## Introduction

Hepatitis C virus (HCV) infection is a major comorbidity in patients with inherited bleeding disorders. Antiviral treatment is administered to such patients to eradicate HCV and prevent the development of severe liver disease. Responses to interferon (IFN)-based therapy for HCV have improved over time by switching from monotherapy to combination therapy with ribavirin (RBV).

## Materials and Methods

We aimed to assess changes in the efficacy of IFN-based therapy for HCV infection in patients with inherited bleeding disorders by retrospectively investigating 147 outpatients in our hospital who received IFN-based therapy for HCV infection from 1992 through 2012 (Fig. 1). Sustained virological response (SVR) was defined as undetectable HCV RNA at the end of treatment and 24 weeks after the therapy.

## Results

Patients included 109 with hemophilia A, 24 with hemophilia B, 9 with von Willebrand disease, and 5 with other bleeding disorders; 45 patients were co-infected with HIV (Table 1). Median age was 37 (range 8-68) years at initial IFN-based therapy. The rate of HCV-genotype 1a, 1b, or mixed was 55% and that of other genotypes without 1a or 1b was 33%. The protocol and doses of IFN-based therapy are shown in Table 2. The proportion of each of the initial protocols is displayed in Fig. 2.

The proportion of patients achieving SVR with initial therapy was 43% (41% in HIV-negative and 47% in HIV-positive patients) (Fig. 3). The initial response did not differ in relation to HIV positivity ($p$=0.85). The rate of relapse was 25% and that of non-response was 30%. According to HCV genotype, SVR for genotype 1a, 1b or mixed was 30%, whereas that for other genotype was 63%. The SVR rate of genotypes in the non-1a/1b group was significantly higher than 1a/1b group ($p$<0.01) (Fig. 7). Rates of success were 26% for IFN monotherapy (12% for IFN-beta, 41% for IFN-alpha, 60% for consensus IFN), 40% for IFN-alpha plus ribavirin, 33% for pegylated (Peg) IFN-alpha monotherapy, and 54% for Peg-IFN-alpha plus RBV (Fig. 4).

Sixty of 84 patients who relapsed or did not achieve virological response after initial treatment underwent several subsequent courses of treatment. Thus, the rate of SVR was 58% (66% HIV-negative and 38% HIV-positive patients) (Fig.5). To achieve SVR, 22 patients were treated twice, 10 thrice, 1 six times, 1 seven times, and 1 eight times (Table 3). The average number of courses of IFN-based therapy per patient was 1.8 in all 147 patients and 1.6 in 98 patients achieving SVR. The proportion of protocols of final IFN-based therapy for these 98 patients is shown in Fig.6.

In total, 67% (70% HIV-negative and 60% HIV-positive patients) of the 147 patients achieved SVR. The SVR rate of HIV-positive patients was lower than that of HIV-negative patients, but the difference was not significant ($p$=0.35). According to HCV genotype, the SVR rate of genotype non-1a/1b reached 92% (97% HIV-negative and 81% HIV-positive patients) (Fig.7).

## Conclusion

The findings of this analysis reconfirm the efficacy of IFN-based therapy for HCV in patients with inherited bleeding disorders. It is suggested that for patients in whom previous anti-HCV therapy has failed, undergoing several courses of treatment can raise the rates of SVR. This is likely to lead to a decrease in the risk of liver fibrosis progression and hepatocellular carcinoma.

## Topics

Medical Topics, Infectious Complications

Table 1 Characteristics of 147 patients with HCV treated by IFN-based therapy

| | | Overall n=147 | HIV-negative n=102 (69%) | HIV-positive n= 45 (31%) |
|---|---|---|---|---|
| Gender | Male (%) | 139 (95) | 94 (92) | 45 (100) |
| | Female (%) | 8 (5) | 8 (8) | 0 (0) |
| Disease | Hemophilia A (%) | 109 (74) | 75 (74) | 34 (76) |
| | Hemophilia B (%) | 24 (16) | 13 (13) | 11 (24) |
| | von Willebrand disease (%) | 9 (6) | 9 (9) | 0 (0) |
| | Other bleeding disorders (%) | 5 (3) | 5 (5) | 0 (0) |
| Age | Median age at 1st IFN therapy (range) | 37 (8-68) | 38 (8-68) | 34 (21-64) |
| HCV viral load | coies/ml | 1.2x10^8 (n=11) | 2.0x10^8 (n=6) | 2.4x10^7 (n=5) |
| | meq/ml | 5.1 (n=1) | 5.1 (n=1) | n.d. |
| | copies/50µl | 10^5.1 (n=11) | 10^5 (n=8) | 10^5.3 (n=3) |
| | KIU/ml | 713 (n=77) | 837 (n=52) | 456 (n=25) |
| | logIU/ml | 6.0 (n=30) | 6.0 (n=22) | 6.1 (n=8) |
| HCV genotype | 1a/ 1b (%) | 81 (55) | 57 (56) | 24 (53) |
| | Non-1a/1b (%) | 48 (33) | 33 (32) | 15 (33) |
| | Unknown (%) | 18 (12) | 12 (12) | 6 (13) |

Table 2 Protocol of anti-HCV treatment with IFN

| Protocol | IFN doses | Year |
|---|---|---|
| IFN-beta | 3-6 MU/day for 4-12 wks + 6 MU/day x 3/wk for 0-20 wks | 1992-2002 |
| IFN-alpha 2a/2b | 3-10 MU/day for 2 wks + 3-10 MU/day x 3/wk for 22 wks | 1992-2009 |
| Consensus IFN-alpha | 12-18 MU/day for 2 wks + 12-18MU x 3/wk for 46 wks | 2002 |
| Peg-IFN-alpha 2a/2b | 80-180 µg/wk for 24-48 wks | 2004-2009 |
| IFN-alpha 2b + RBV* | 3-6 MU/day for 2 wks + 3-6 MU/day x 3/wk for 22 wks | 2001-2003 |
| Peg-IFN-alpha 2a/2b + RBV* | 80-180 µg/wk for 24-72 wks | 2004-2012 |

*RBV dose is 600-1000 mg/day

Fig. 1 Initial IFN-based therapy for HCV in 147 patients during 1992-2012.

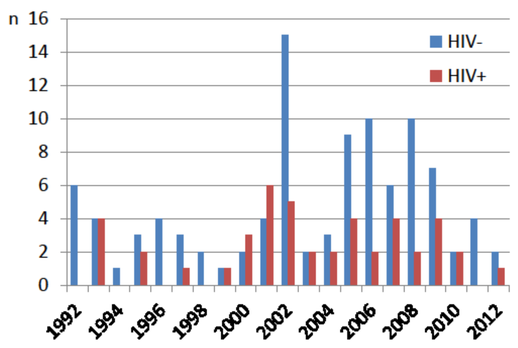



Fig. 2 Proportion of protocol of initial IFN-based therapy.

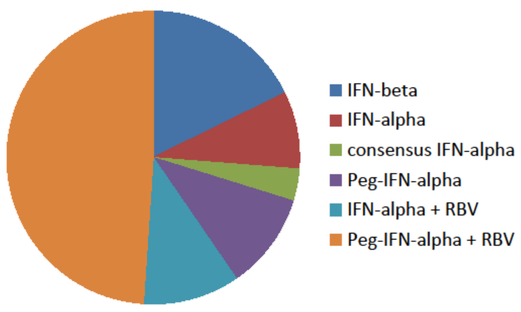



Fig. 3 Virological response to initial IFN-based therapy for HCV in 147 patients.

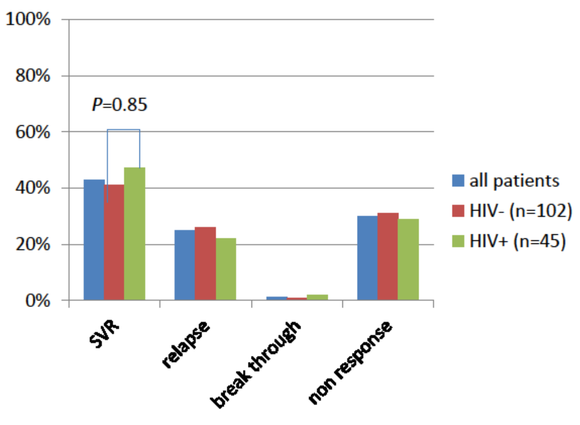



Fig. 4 SVR rate among protocols of initial IFN-based therapy.

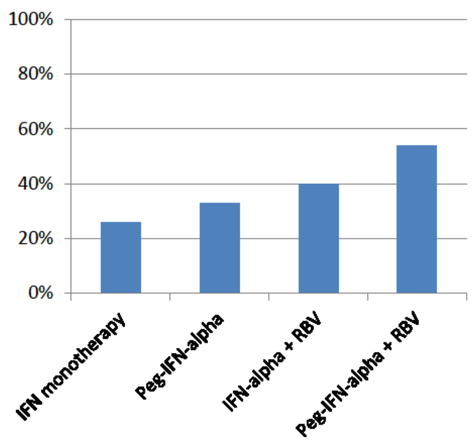



Table 3 SVR to initial treatment and retreatment by IFN for HCV

| | | Initial | Retreatment | | | | | | | | Average* | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 1st | 2nd | 3rd | 4th | 5th | 6th | 7th | 8th | Sub-total | | |
| HIV- | n | 102 | 44 | 21 | 9 | 5 | 5 | 4 | 1 | 44 | 1.9 | 102 |
| | SVR | 42 | 18 | 8 | 0 | 0 | 1 | 1 | 1 | 29 | 1.7 | 71 |
| | % | 41 | 41 | 38 | 0 | 0 | 20 | 25 | 100 | 66 | | 70 |
| HIV+ | n | 45 | 16 | 5 | 3 | 2 | 1 | | | 16 | 1.6 | 45 |
| | SVR | 21 | 4 | 2 | 0 | 0 | 0 | | | 6 | 1.3 | 27 |
| | % | 47 | 25 | 40 | 0 | 0 | 0 | | | 38 | | 60 |
| Total | n | 147 | 60 | 26 | 12 | 7 | 6 | 4 | 1 | 60 | 1.8 | 147 |
| | SVR | 63 | 22 | 10 | 0 | 0 | 1 | 1 | 1 | 35 | 1.6 | 98 |
| | % | 43 | 37 | 38 | 0 | 0 | 17 | 25 | 100 | 58 | | 67 |

*average number of courses of IFN-based therapy per person

Fig. 5 Results of SVR rate to IFN-based therapy for patients with HCV.

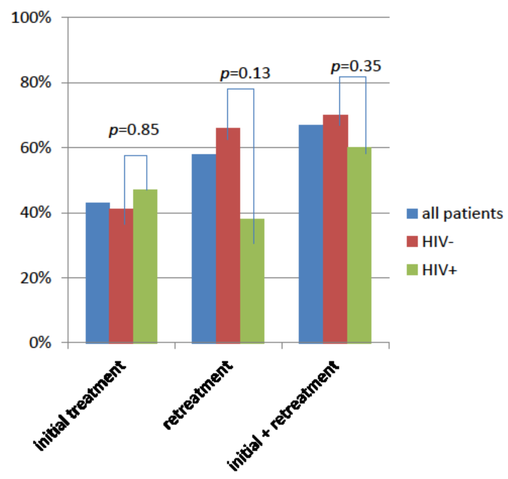



Fig. 6 Proportion of protocol of final IFN-based therapy for 98 patients who achieved an SVR.

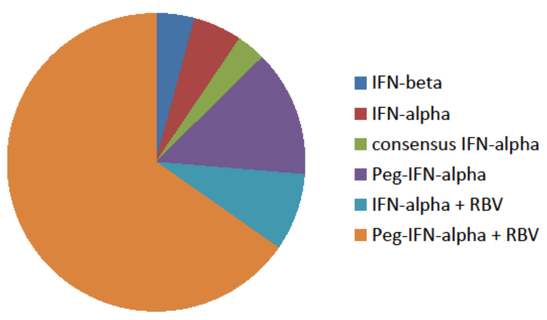
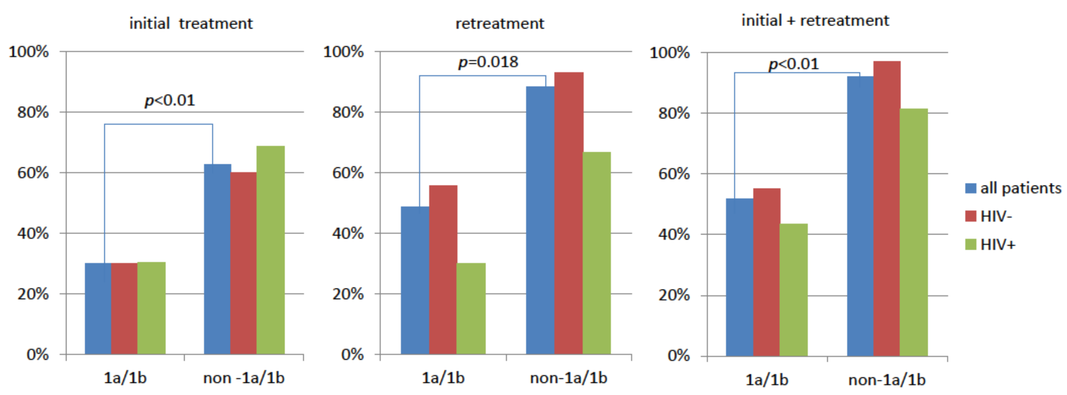



Fig. 7 SVR rate of IFN-based therapy for HCV in genotype 1a/1b versus non-1a/1b.




WFH2014
92--P-M
Infectious Complications
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DOI: 10.3252/pso.eu.WFH2014.2014
Poster presented at: WFH 2014 WORLD CONGRESS Melbourne, Australia, May 11-15
PosterSessionOnline.com