EDITORIAL

Acute Hepatitis C: in Search of the Optimal Approach to Cure

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Acute viral hepatitis (AVH) due to HCV infection has nowadays changed its pattern of presentation and clinical course. Posttransfusion AVH, with a chronicity rate of up to 86%,[1] has disappeared from the Western world, where at present the majority of cases seen in practice, referred to as "community-acquired sporadic infection", are acquired by intravenous drug use (IVDU) or by non-apparent parenteral exposure due to sexual contact or medical and cosmetic procedures. Contagion through the latter modalities tends to cause a clinically symptomatic illness with jaundice, with a self-limited course in the majority of cases[2]; the clinical expression of disease depends mostly upon host factors.[3] Overall, overt AVH due to sporadic HCV infection has a reported rate of chronicity of about 50%, clearly lower than the post-transfusion cases. Whether the different rate of progression to chronic infection is due to the smaller size of the inoculum[4] or other inapparent cofactors is unclear,[3] regardless of whether the need for immediate treatment of all acute cases is decreased.

The epidemiology of acute hepatitis C is also changing, affecting mostly injection drug users, who are less suitable to undergo treatment.[5] Also, some studies indicate that even in countries where genotype 1 is prevalent, many patients with acute hepatitis C have genotype 3 infection, which has a higher trend to spontaneous resolution[6,7] and a response rate in excess of 80 % even on short treatment courses.[8,9] Thus, it would seem reasonable to defer treatment in acute AVH because of genotype 3.

Last but not least, diagnosis of acute HCV infection may be problematic, because serological markers cannot reliably distinguish acute hepatitis C from an exacerbation of chronic HCV infection. Although serial assessment of IgM anti-HCV titres may help,[10] this test is not readily available, and only evaluation of the viral kinetics in the first weeks after presentation is really predictive of spontaneous clearance.[11]

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Since 2001, when a cohort study by Jaeckel et al.[12] demonstrated that 6 months of treatment with standard IFN alfa 2b at doses comparable to those used for chronic hepatitis was enough to eradicate HCV infection in 98% of patients with acute hepatitis C, the issue of optimal treatment of AVH due to HCV has been a matter of hot debate. Albeit a fair number of studies (reviewed by meta-analysis in [13]) show a net benefit of IFN therapy over no treatment in terms of duration of viraemia, rate of chronicity, and duration of biochemical alterations, there is still no consensus on whom to treat and the timing of treatment. This is reflected by a lack of precise recommendations in the most recent consensus statements from the NIH[14] and EASL.[15]

Large randomized trials should form the basis of guidelines for clinical management and treatment, and have been advocated,[16] but will probably never be performed owing to the complexity of the population to be studied, the rarity of this condition, the acute nature of disease, and also the attitude favouring early treatment of many clinicians.

In this issue of HEPATOLOGY, Wedemeyer and colleagues[17] report the final results of an open, uncontrolled multicenter trial of early monotherapy of PEG IFN alfa 2b as treatment for acute hepatitis C. They evaluated 89 patients with acute hepatitis C collected from 53 different German centers and coordinated within the network of the HEP-NET Study House. Infection in these patients was caused by intravenous drug abuse, sexual transmission, medical procedures, needlestick injuries and other potential modes (tattooing, acupuncture), 2/3 of cases being infected by HCV genotype 1. All patients in the study received PEG IFN alfa 2b at a dose of 1.5 μg/kg once weekly for 6 months. Treatment was initiated after an average of 76 days (range 14-150 days) from the presumed exposure, although no mention is made of the interval between clinical presentation and the start of therapy[3]).

Surprisingly, the results obtained were worse than those of Jaeckel et al.[12] In fact, an end-of-treatment response (ETR), was reached by 82% of all patients, and only 71% had a sustained virological response (SVR). By comparison, Jaeckel et al.[12] treated 44 patients from 24 centers with 5 MU of IFN alfa 2b daily for 4 weeks and then twice weekly for 20 weeks obtained an ETR of 98% and an SVR of 98%. Use of the induction dosage in Jaeckel's study obtained an early viral clearance at 4 weeks

of therapy in 72% of patients. No data at 4 weeks are available from the Wedemeyer study, but the low rate of response appears to be mostly due to a high rate of nonadherence to the study protocol: 21% (19/89) of the patients did not take at least 80% of the intended PEG IFN dosage for 80% of the scheduled period, many of them being actually lost from the study either during treatment (8/19) or during follow-up (5/19). If the response rate was evaluated not by intention-to-treat, but per protocol, the rates of EVR and SVR increased to 94% and 89%, respectively. Further analysis[19] shows that the major determinant of loss to follow-up was a low social background with contact to the drug scene, but not direct drug abuse.

This trial highlights well the difficulties facing clinicians who wish to perform trials of treatment of this condition. Regarding the enrollment, it took 3 years and 53 centers, to recruit 89 patients. It is possible that a sizable number of potential candidates were not enrolled into the study because of projected non-compliance or HIV coinfection. Some patients with "uncertain diagnosis" may have been excluded, whereas others may have been included even though they had chronic infection owing to the tight time frame preventing confirmatory testing.

Another relevant issue is the number of patients treated at each center: because the average number of subjects per center was 1.7, many sites must have actually enrolled only one case. Variations in follow-up protocol and physician's experience might account for the high number of dropouts. It is notable, however, that in the Jaeckel's study, where each center had enrolled on average 1.8 patients, only 1 of 44 patients did not adhere to the protocol. Because a number of centres were involved in both studies, and the patient populations have similar sociodemographic features, it is unclear what caused the difference in compliance.

The large number of dropouts in Wedemeyer's study also causes problems in the interpretation of results. It is not clear if those 19 (21%) who did not fulfill the criteria of adherence to treatment, were comparable to the 70 who managed to stay on schedule. In fact, their different socioeconomic background[19] may by itself be a determinant of a worse outcome. Thus, the results of this study may not be generalizable.

In this study, IVDUs accounted for 22% of the population, and half of them were lost to follow-up. As previously shown by Broers,[5] IVDUs have a low tolerance and adherence to IFN regimens, especially for women or for those with ongoing drug abuse. IVDUs are fragile patients; IFN therapy for acute hepatitis may be associated with a high incidence of psychiatric side effects leading to treatment interruption and adverse psychosocial outcomes. The rationale to treat IVDUs in the acute phase must hence be very carefully weighed against the likelihood of spontaneous resolution.

When, whom, and how to start treatment remains a core issue.[21] Trials performed between 1991 and 2002 were highly heterogeneous in this respect, as treatment was started at widely variable intervals after the clinical onset of AVH. In order to overcome heterogeneity, we have performed a meta-analysis of controlled trials[13] to define the best timing and the optimal treatment strategy to avoid chronicity of HCV infection while reducing treatment to a minimum. Twelve trials were analyzed (414 patients). The overall rate of chronicity in untreated subjects was very high, ranging from 65% to 75%, due to the high number of cases with posttransfusion hepatitis included. IFN significantly increased the SVR (risk difference 49%; 95% CI 32.9%-65%) compared to no treatment. The risk difference of SVR increased from 5% to 90% when trials were ordered by increasing interferon weekly dose. A daily induction dose during the first month was the best option of treatment. Delaying therapy by 8 to 12 weeks after the onset of disease did not compromise the SVR rate.

Given that starting treatment at a slightly later stage of acute infection does not seem to compromise the ultimate rate of SVR, the key point is whether all patients with acute hepatitis C should receive immediate treatment or if a "wait and see" strategy should be adopted to identify subjects with spontaneous viral clearance. Santantonio et al.,[22] in a prospective long-term study of 16 untreated patients, observed that the rate of chronicity was higher in asymptomatic than in symptomatic patients and that in most instances spontaneous viral clearance occurs within 8 to 12 weeks from the onset of the disease. These data support the observations made by Gerlach and Hofer[2] of a close relationship between a more severe, symptomatic clinical course and a better likelihood of early spontaneous viral clearance.

Nomura et al.[22] recently reported a randomized controlled trial of 30 patients with acute hepatitis C. Patients in the early-intervention group received, 8 weeks after the onset of acute hepatitis, IFN alfa n3 6 MU daily for 4 weeks, while therapy (IFN alfa n3 6 MU daily for 4 to 20 weeks) was initiated after 1 year of observation in the late-intervention group or in case of recrudescence of disease in the early-intervention group. The SVR rate was significantly higher in the early-intervention group (87%, 13 of 15 patients after short-term therapy alone, and 100% after follow-up retreatment) than in the late-intervention group (53%, 8 of 15 patients after short-term therapy with or without follow-up therapy). Thus this trial, in accordance with our meta-analysis,[13] shows that delaying therapy up to 8 weeks after onset does not affect

the SVR rate. Delaying the start of therapy would in fact avoid unnecessary treatment of those patients who would spontaneous clear the virus. In fact, among 15 consecutive patients with acute hepatitis C observed over the last 2 years at our Unit, all with an iatrogenic exposure and documented anti-HCV seroconversion, 11 patients (73.3%) cleared spontaneously HCV within 12 (mean 10.4) weeks (unpublished data). In Wedemeyer's study, treatment was initiated after a median of 76 days after infection (range 14-150). Assuming a median of 46 days between exposure and first elevation of ALT,[3] the time interval reported suggests that early treatment was initiated in most cases without any "wait and see" strategy. In the absence of an untreated control group, it is impossible to know what is the real gain in terms of viral clearance obtained by IFN treatment.

Ideally, one would like to treat an acute condition with the shortest possible schedule. Unfortunately, Wedemeyer's study was non-contributory. Regarding duration, data from meta-analyses of trials would indicate that either 12 weeks [24] or 16 to 24 weeks[13] of treatment with IFN monotherapy are the best choice, whereas the more recent trial by Nomura et al.[23] suggests that short-term (4 weeks) IFN treatment of patients with acute hepatitis C may be associated with satisfactory results, if initiated at an early stage of the disease. Whether ethnic differences and the use of different types of IFNs may account for the good response is unclear. As to the issue of dosing, higher amounts of IFN during the first weeks of therapy seem to be the most effective approach. In the trial by Jaeckel et al.,[12] a regimen of 5 MU of IFN once a day for 4 weeks followed by 5 MU of IFN twice weekly for 20 weeks achieved SVR in almost all patients. Similar results were obtained by Delwaide et al.,[25] who used the same high induction dose. Our meta-analysis[13] provides further evidence that treatment with a daily dose of standard IFN is the best option for obtaining a SVR. All these studies have used non-pegylated IFN alfa and tried to optimize pharmacodynamics by giving it daily. The real issue, in the age of PEG IFNs, is whether results can be reproduced by once-weekly regimens. Comparability of dosages between standard and PEG IFNs is also a matter of concern.[26] Before Wedemeyer's study, at least three trials of treatment of acute hepatitis C with Peg-IFN alfa 2b 1.5 μg/kg per week for 12 to 24 weeks[5,27,28] have been reported over the last 2 years. The rate of SVR ranged from 57%,[5] in a study with the highest rate of non-compliance to 71%[28] and 94%[27] on a 24 weeks regimen. In all studies, genotype 2 or 3 was the most important factor of response in adherent patients. Wedemeyer's reported SVR rate of 82% fits into this range, confirming that the PEG IFNs, with their ease of use and a response rate which is comparable overall to standard IFNs, are currently the best therapeutic option for acute hepatitis C. It still remains to be assessed if it is possible to use less IFN, either from inception or after the first 4 weeks. Lower dose may be of outmost importance, since one of the main reasons for non-adherence in Wedemeyer's group of patients were psychiatric symptoms, usually linked to the use of high doses of IFN.

Will the combination with ribavirin help to raise the SVR? Data from a small study[29] with standard IFN without or with ribavirin do not suggest any improvement in efficacy. Other ongoing studies (Santantonio, personal communication) show a similar trend. Becausethe rate of SVR to monotherapy is already very high in patients who comply to an adequate regimen, it is unlikely that the addition of ribavirin, a drug whose side effects are a major reason for non adherence when treating chronic hepatitis C, will improve the results in patients with AVH. Theoretically, combination therapy could be desirable for difficult-to-treat genotypes or for those with HIV coinfection.[20]

In conclusion, there are still more questions than answers. In general, IFN monotherapy for acute hepatitis C can be supported, but a strategy taking into account both baseline (clinical presentation, genotype, HIV coinfection) and early (spontaneous viral decay) virological response should be developed from carefully conducted, controlled prospective studies comparing a "wait and see strategy",[30] and different schedules of PEG IFN monotherapy to optimize adherence and costs and to reduce the number needed to treat. The price of the ultimate success of therapy for AVH due to HCV, *i.e.*, a stable and definitive clearance of HCV with no residual liver disease in the long term,[31] should not be paid by a high number of patients who are treated needlessly.

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References

1. Wiese M, Grungreiff K, Guthoff W, Lafrenz M, Oesen U, Porst H. East German Hepatitis C Study Group. Outcome in a hepatitis C (genotype 1b) single source outbreak in Germany—a 25-year multicenter study. J Hepatol 2005;43:590-598.
2. Gerlach JT, Diepolder HM, Zachoval R, Gruener NH, Jung MC, Ulsenheimer A, et al. Acute hepatitis C: high rate of both spontaneous and treatment-induced viral clearance. Gastroenterology 2003;125:80-88.
3. Mosley JW, Operskalski EA, Tobler LH, Andrews WW, Phelps B, Dockter J, et al. Viral and host factors in early hepatitis C virus infection. HEPATOLOGY 2005;42;86–92.
4. Farci P, Shimoda A, Coiana A, Diaz G, Peddis G, Melpolder JC, et al. The outcome of acute hepatitis C predicted by the evolution of the viral quasispecies. Science 2000 14;288:339-344.

5. Broers B, Helbling B, Francois A, Schmid P, Chuard C, Hadengue A, Negro F. Swiss Association for the Study of the Liver (SASL 18). Barriers to interferon-alpha therapy are higher in intravenous drug users than in other patients with acute hepatitis C. J Hepatol 2005;42:323-328.
6. Hwang SJ, Lee SD, Lu RH, Chu CW, Wu JC, Lai ST, et al. Hepatitis C viral genotype influences the clinical outcome of patients with acute post-transfusion hepatitis C. J Med Virol 2001;65:505-509.
7. Lehmann M, Meyer MF, Monazahian M, Tillmann HL, Manns MP, Wedemeyer H. High rate of spontaneous clearance of acute hepatitis C virus genotype 3 infection. J Med Virol 2004;73:387-391.
8. Mangia A, Santoro R, Minerva N, Ricci GL, Carretta V, Persico M, et al. Peginterferon alfa-2b and ribavirin for 12 vs. 24 weeks in HCV genotype 2 or 3. N Engl J Med 2005;352:2609-2617.
9. von Wagner M, Huber M, Berg T, Hinrichsen H, Rasenack J, Heintges T, et al. Peginterferon-alpha-2a (40KD) and ribavirin for 16 or 24 weeks in patients with genotype 2 or 3 chronic hepatitis C. Gastroenterology 2005; 129:522-527.
10. Sagnelli E, Coppola N, Marrocco C, Coviello G, Battaglia M, Messina V, et al. Diagnosis of hepatitis C virus related acute hepatitis by serial determination of IgM anti-HCV titres. J Hepatol 2005;42:646-651.
11. Hofer H, Watkins-Riedel T, Janata O, Penner E, Holzmann H, Steindl-Munda P, et al. Spontaneous viral clearance in patients with acute hepatitis C can be predicted by repeated measurements of serum viral load. HEPATOLOGY 2003;37:60-64.
12. Jaeckel E, Cornberg M, Wedemeyer H, Santantonio T, Mayer J, Zankel M, et al. Treatment of acute hepatitis C with interferon alfa-2b. N Engl J Med 2001;345:1452-1457.
13. Licata A, Di Bona D, Schepis F, Shahied L, Craxi A, Camma C. When and how to treat acute hepatitis C? J Hepatol 2003;39:1056-1062.
14. NIH Consensus Statement on Management of Hepatitis C: 2002. NIH Consens State Sci Statements. 2002;19(Jun 10–12):1-46.
15. Proceedings of the European Association for the Study of the Liver (EASL) International Consensus Conference on Hepatitis B. September 14–16, 2002. Geneva, Switzerland. J Hepatol 2003;39(Suppl 1):S1-S235.
16. Zekry A, Patel K, McHutchison JG. Treatment of acute hepatitis C infection: more pieces of the puzzle? J Hepatol 2005;42:293-296.
17. Wedemeyer H, Wiegand J, Buggisch P, Boecher W, Zeuzem S, Gelbmann C, et al. Early monotherapy with peginterferon alfa-2b for acute hepatitis C infection: The HEP-NET Acute-HCV-II Study. HEPATOLOGY 2006;43: 250-256.
18. Lindsay KL, Trepo C, Heintges T, Shiffman ML, Gordon SC, Hoefs JC, et al. A randomized, double-blind trial comparing pegylated interferon alfa-2b to interferon alfa-2b as initial treatment for chronic hepatitis C. HEPATOLOGY 2001;34:395-403.
19. Wiegand J, Buggisch P, Boecher W, Zeuzem S, Gelbmann C, Berg T, et al. Relevance of adherence in the treatment of acute hepatitis C infection: final results of the German HEP-NET Acute Hepatitis C II Trial. HEPATOLOGY 2005;42(Suppl 1);647A.
20. Gilleece YC, Browne RE, Asboe D, Atkins M, Mandalia S, Bower M, et al.Transmission of hepatitis C virus among HIV-positive homosexual men and response to a 24-week course of pegylated interferon and ribavirin. J Acquir Immune Defic Syndr 2005;40:41-46.
21. Wedemeyer H, Jackel E, Wiegand J, Cornberg M, Manns MP. Whom? When? How? Another piece of evidence for early treatment of acute hepatitis C. HEPATOLOGY 2004;39:1201-1203.
22. Santantonio T, Sinisi E, Guastadisegni A, Casalino C, Mazzola M, Gentile A, et al. Natural course of acute hepatitis C: a long-term prospective study. Dig Liver Dis 2003;35:104-113.
23. Nomura H, Sou S, Tanimoto H, Nagahama T, Kimura Y, Hayashi J, et al. Short-term interferon-alfa therapy for acute hepatitis C: a randomized controlled trial. HEPATOLOGY121 2004;39:1213-9.
24. Vogel W. Treatment of acute hepatitis C virus infection. J Hepatol 1999; 31(Suppl 1):189-192.
25. Delwaide J, Bourgeois N, Gerard C, De Maeght S, Mokaddem F, Wain E, et al. Treatment of acute hepatitis C with interferon alpha-2b: early initiation of treatment is the most effective predictive factor of sustained viral response. Aliment Pharmacol Ther 2004;20:15-22.
26. Vyas K, Brassard DL, DeLorenzo MM, Sun Y, Grace MJ, Borden EC, et al. Biologic activity of polyethylene glycol12000-interferon-alpha2b compared with interferon-alpha2b: gene modulatory and antigrowth effects in tumor cells. J Immunother 2003;26:202-211.
27. Santantonio T, Fasano M, Sinisi E, Guastadisegni A, Casalino C, Mazzola M, et al. Efficacy of a 24-week course of PEG-interferon alpha-2b monotherapy in patients with acute hepatitis C after failure of spontaneous clearance. J Hepatol 2005;42:329-333.
28. Talleri G, Cariti G, Gaiottino F, De Rosa F, De Blasi T, Audagnotto S, et al. Three months course of PEG IFN alfa 2b in acute HCV hepatitis [Abstract]. HEPATOLOGY 2004;40(Suppl 1);179A.
29. Rocca P, Bailly F, Chevallier M, Chevallier P, Zoulim F, Trepo C. Early treatment of acute hepatitis C with interferon alpha-2b or interferon alpha-2b plus ribavirin: study of sixteen patients Gastroenterol Clin Biol 2003;27:294-299.
30. Pimstone NR, Pimstone D, Saicheur T, Powell J, Yu AS. "Wait-and-see": an alternative approach to managing acute hepatitis C with high-dose interferon-alpha monotherapy. Ann Intern Med 2004;141:W91-W92.
31. Wiegand J, Jackel E, Cornberg M, Hinrichsen H, Dietrich M, Kroeger J, et al. Long-term follow-up after successful interferon therapy of acute hepatitis C. HEPATOLOGY 2004;40:98-107.