# Treatment of chronic hepatitis C with interferon in combination with other compounds

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## Introduction

Although the natural history of hepatitis C and its long term sequelae start to be documented, its physiopathology remains poorly understood. It is clear however that HCV like HBV is not cytopathic by itself and that the liver lesions are immunologically mediated. More than 20% of HCV infected individuals do not progress despite high levels of circulating virus. HCV RNA by itself is therefore not a good enough marker for measuring drug activity on this disease. When the first therapeutic studies with IFN in hepatitis C were conducted and registration granted, HCV RNA monitoring was not yet available (1). End points used for clinical trials were therefore liver function tests and especially AST/ALT and liver histology.

Since that time HCV RNA levels has become the first parameter used for evaluating the efficacy of drugs against HCV.

Over the last 15 years Interferon alpha (IFN a) has been confirmed as the pivotal treatment for hepatitis C (1). However its efficacy remains unsatisfactory (1-2). Interestingly many patients treated with IFN do normalise their ALT and/or improve their liver histology while fewer do clear the virus (2). This further documents that HVC RNAS should not be the sole end point of therapy.

Ribavirin and IFN combination has become the standard of care for naive and relapsers after a first course of IFN (3). Unfortunately its efficacy in patients who failed to respond to IFN does not seem as promising (4). Alternative approaches are therefore needed.

## Amantadine and rimantadine in combination with IFN

Although a preliminary study suggested encouraging results (5), later, monotherapy studies demonstrated little or no efficacy (6-11) and combination therapies with IFN may be more promising. In a randomized clinical trial of alpha interferon for non-responders or relapser chronic hepatitis C patients, end-of treatment virologic response was observed in 5/16 (3 1,3%) patients administered rIFN-α2a/amantadine, compared with only 2/28 (7,7%) patients treated with rIFN-α2a monotherapy. Studies that have directly compared the efficacy of rIFN-α2b/ribavirin with that of IFN amantadine in the treatment of alpha interferon nonresponders indicate that virologic response rates (HCV-RNA negativity at 12 weeks of therapy) may be comparable between the two combinations but sustained response may even be less for amantadine IFN combination.

## Triple therapy with IFN plus ribavirine and amantadine

The efficacy of triple therapy with alpha interferon, ribavirin and amantadine was recently evaluated by Brillanti et al in a study of 20 alpha interferon nonresponders (12). Patients were randomized to either combination therapy with rIFN-α2b (3 MIU TIW) plus ribavirin (800 to 1,000mg daily) or to triple therapy with rIFN-α2b (3MIU TIW), ribavirin (800 to 1,000 mg daily), and amantadine (100 mg daily). A virologic ETR occurred in 1/10 (10%) patients in the combination rIFN-α2b/ribavirin therapy group and in 7/10 (70%) patients in the triple therapy group. Six month after the end of therapy serum HCV RNA was undetectable in three of the seven patients with virological response at the end of treatment, treated by triple antiviral therapy, while viremia reappeared during the follow up period in the only one patient treated with double therapy who had become HCV RNA negative during treatment.

Disappearance of HCV RNA was associated with a return to normal of ALT levels. Despite recurrence of HCV replication, one patient treated by triple antiviral therapy maintained normal ALT levels. In contrast for the other patients for whom reappearance of serum HCV RNA was accompanied by ALT reactivation.

Note that these therapies were generally well tolerated. No serious adverse events occurred, and the side effects (mild headache, ribavirin induced heamolysis) were fully reversible after therapy cessation.

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## Ursodeoxycholic acid combined with IFN

– Monotherapy

Although several double-blind, placebo-controlled studies of UDCA mono-therapy have been carried out which all show a very significant effect on the biochemical variables with an improvement of the transaminases of 25-50% compared to the initial values occurs, a full biochemical remission is never archieved and viremia is not abated (13).

– Combination

So far 14 studies have been published, in which the role of UDCA as adjuvant therapy with IEN-α was investigated. Seven of the these studies clearly show a more sustained prolonged response after IFN/UDCA combination treatment. On the long term (more than 12 months after cessation of therapy), however this effect does not seem to be sustained.

The final conclusion is therefore that adjuvant therapy of UDCA with IFN-α treatment in hepatitis C has a marginal effect and it remains to be seen whether this "anti inflammatory" effect is truly worthy. Documentation of the histological benefit in non- responder for example is missing.

– Alternative approach using IL10 for treating non-responders

IL-10 is a cytokine which downregulates the pro-inflammatory Thl response and might thereby reduce cellular injury in patients with chronic HC. In a murine fibrosis model, IL-10 has also been shown to inhibit fibrogenesis.

24 patients who failed IFN therapy were treated with either 4 or 8.μg/kg rIL-10 daily for 90 days and were evaluated with liver biopsy performed before and at the end of treatment. RIL-10 was well tolerated and 22/24 patients completed the study.

Serum ALT levels normalized in 19/22 patients at the end of therapy.

Compared liver biopsies showed a decrease of hepatic inflammation in 19/22 patients and decrease of Ishak Fibrosis score in 14/22 with a mean change from 3,6 +/- 04 to 2,6+/-0,4. No change of in HCV RNA was observed.

IL-10 therapy was also associated with changes in serum immune response and fibrosis markers.

Recombinant IL-10 is safe and could normalize ALT, improve liver histology and reduce liver fibrosis. Further studies are necessary to confirm these preliminary results which do suggest that IL-10 may have therapeutic potential in patients with chronic hepatitis C and extensive fibrosis and therefore offer a unique alternative for non-responder patients.

## Combination of IFN whith non-steroidal anti-inflammatory drugs (NSAIDS)

The rationale for such regimen is related to the potential increase of the enzyme 2'5' oligoadenylate synthetase which mediates the antiviral effects of IFN supposedly resulting from the inhibition of prostaglandin synthesis by NSAIDS. Although this was a theoretically attractive possibility it was not confirmed since.

Two studies using tenoxican or ketoprofen failed to demonstrate any biochemical histological or virological benefit (15-16).

Importantly a relatively high incidence of gastric ulcerations during treatment have been observed and clearly this approach should no longer be used.

## Conclusion

Because of its high prevalence and significant morbidity hepatitis C is likely to become the leading cause of liver disease and associated complications over the next 2 decades. Combination therapy including IFN appears as the most promising and rationale approach to improve actual results. So far the most successful is still ribavirin together with IFN.

Triple therapy with amantadine variants to be further novel approaches such as IL10 are amently has evaluated as well.

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