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Editorial

Amantadine for chronic hepatitis C: a magic bullet or yet another dead duck?

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Dissatisfaction with the results of antiviral therapy for chronic hepatitis C fuels continuous research for more effective and tolerable regimens. Debate has recently been focused on the possible use of amantadine (AMA), an agent with direct activity against RNA viruses, to enhance the effects of interferons. Two papers [27,28] add to the controversy.

AMA (1-aminoadamantan), a tricyclic amine, and its related analogue rimantadine (RIMA) have antiviral activity against toga, myxo, arena, flavi, and coronaviruses [1,2]. Inhibition of influenza A virus replication obtained with these drugs has been exploited clinically to prevent and to cure flu. Known mechanisms of action of AMA include inhibition of an early step in viral replication, most likely viral uncoating and interaction with the influenza A viral matrix protein (M2), which is important in virion budding [1].

In 1997, J.P. Smith reported, in a pilot study of 22 patients with chronic hepatitis C who had failed previous monotherapy with α-interferon (IFN) [3], that AMA was effective in reducing necroinflammation, with 64% of patients having a decrease in aminotransferases on therapy. Six patients had normal alanine aminotransferase (ALT) and negative hepatitis C virus (HCV)-RNA at the end of therapy, and four had a sustained response (SR) [4]. The effectiveness of these tricyclic amines as antiviral agents against HCV was challenged by subsequent trials of AMA [5–11] and of RIMA [12], both in non-responders to IFN and in naïve patients. These studies have shown almost uniformly some reduction of ALT, ranging from 0 to 58% of patients while on therapy, but no consistent effects on HCV-RNA. SR to AMA monotherapy has never been reported after the original study [3]. The behaviour of AMA is similar to ribavirin, which, in monotherapy, often improves liver biochemistry [13] but does not significantly reduce the HCV viral load [14].

The absence of suitable cellular models of HCV replication has hampered the in vitro evaluation of AMA and RIMA. Indirect assessment of their effects on HCV protease, helicase, ATPase, RNA-dependent RNA polymerase, and HCV internal ribosomal entry site (IRES) translation has been performed by in vitro biochemical assays [15]. No inhibition (>15%) was observed with concentrations up to 400 μg/ml. IRES-specific inhibition was not seen at clinically relevant concentrations. Cap and IRES reporter genes were suppressed at higher levels, possibly by non-specific translation inhibition. These experiments allowed to conclude that AMA and RIMA have no direct specific inhibitory effect against HCV non-structural proteins and IRES in vitro. A mammalian binary expression system able to synthesize positive and negative strand HCV-RNA [16] has recently been used to determine whether IFN, ribavirin, and AMA directly inhibit HCV replication. In this replicon system, rIFN-α-2b induced a dose-responsive inhibition of HCV (−) strand synthesis without affecting actin and β-galactosidase mRNA levels. The same doses produced complete inhibition of HCV protein synthesis. Ribavirin and AMA, at doses above pharmacological concentrations, had no effect on HCV (−) RNA levels. Thus, while IFN acts directly as an anti-HCV agent, ribavirin and AMA actions against HCV are likely to be indirect.

Like ribavirin, AMA and RIMA may act also on the immune system. The effects of AMA and rIFN-α-2b alone and combined have been studied in cultured PBMC from 15 chronic hepatitis C patients and ten controls [17]. Four patients (27%) had HCV core and NS3-specific proliferative responses. AMA suppressed these responses in all cases with an antiproliferative effect greater than IFN. All PBMC cultures from patients were HCV-RNA positive. AMA, alone or combined with IFN, dose-dependently reduced the HCV-RNA content. With AMA alone, IFN

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alone and their combination, 7, 13 and 20% of PBMC cultures became HCV-RNA negative, respectively. In contrast to IFN, AMA did not modify the expression of 2′,5′-OAS or the spontaneous or mitogen-stimulated production of γ-IFN and interleukin 10.

AMA and RIMA are thus very weak antivirals providing some anti-inflammatory activity. The lack of more potent direct inhibitors of HCV replication suitable for clinical use has nonetheless stimulated studies aimed at evaluating the potential of combination therapy between IFN and AMA, both in non-responders to IFN or IFN and ribavirin [18–23] and in naïve patients [24,25]. Many other controlled and uncontrolled trials are in progress.

Two recently reported trials have reached contrasting results. Zeuzem and colleagues [24] studied 119 naïve subjects with chronic hepatitis C, randomly allocating them to IFN-α-2a at 6 MU t.i.w. for 24 weeks, then 3 MU t.i.w. for another 24 weeks plus AMA sulphate at 100 mg twice daily p.o. for 48 weeks, or to the same IFN regimen plus placebo. A virological, end-of-treatment response (ETR) was observed in 34% of patients treated with the combination therapy and in 33% on monotherapy, while a SR occurred in 10 and 22%, respectively. Mangia and colleagues [25], who enrolled 200 naïve patients and randomized them to 48 weeks of treatment with IFN-α-2a at 6 MU t.i.w. for 48 weeks with or without AMA hydrochloride at 100 mg twice daily, reported more optimistic findings. The rate of ETR in their study was 45.5% for combination and 28.7% for monotherapy, and more importantly, that of SR was 29.3 vs. 16.8%, respectively. Interestingly, in both studies, the addition of AMA did not affect the safety and tolerability profile of IFN. The health-related quality of life [26] was seemingly improved, in terms of fatigue and vigour scores by the antidepressant action of AMA. Even accounting for some differences among the trials in the IFN schedule, the distribution of HCV genotypes and the rate of advanced fibrosis, a strong determinant of low responsiveness to IFN, it is difficult to reconcile the discordant results of these trials. Scarce information can be derived from the other studies, many with confoundingly small sample sizes and reported only in abstract.

Two large studies [27,28] add some relevant elements to the pattern. In the first, ref. [27], produced by a cooperative UK group after a small pilot trial at one of the centres involved, a total of 179 naïve patients (pilot + multicentre studies), 9% with cirrhosis and an unusually low 32% of genotype 1, were randomized to receive IFN-α-2a at 4.5 MU t.i.w. for 48 weeks with or without AMA hydrochloride at 100 mg twice daily. ETR rates were 31% for combination and 19% for monotherapy, and SR rates were 23 and 17%, respectively. In the other study [28], a multicentre Italian trial, 180 naïves without cirrhosis were randomized to IFN-α-2a at 6 MU t.i.w. for 24 weeks, then 3 MU t.i.w. for another 24 weeks with or without AMA hydrochloride at 100 mg twice daily for 48 weeks. The results were again uninspiring, with an ETR of 47% for the combination and 37% for monotherapy and an SR of 24 vs. 17%. A negative effect of genotype 1 on responsiveness was seen in the two studies, reiterating the findings by Zeuzem and Mangia.

Is then AMA another failed promise? Possibly, but the case is still open. An interesting finding in both studies [27,28] is that at 3 months of treatment, patients on the combination are significantly more likely to be HCV-RNA negative (62 vs. 47% in the UK study, 61 vs. 46% in the Italian study). These figures, which are consistently higher than the ETR, suggest that an initial additive effect of AMA exists, and helps to reduce temporarily the viral load to undetectable levels. This weak effect is then lost, possibly by viral escape mutations, while still on treatment, thus bringing the final result down to the level of IFN monotherapy. In a similar trial still underway, we have observed the same phenomenon, and found a reduction in the heterogeneity of the re-emerging quasispecies of subjects with a breakthrough (Di Marco, unpublished data). AMA thus probably has some anti-HCV effect, but readily induces viral resistance leading to a loss of efficacy.

Should we discard the feeble antiviral activity of AMA and RIMA? In naïve patients, AMA is already a loser when, in combination with IFN, it is compared with the standard IFN–ribavirin schedule with its 41% rate of SR [29]. Pegylated IFNs, whose rate of success in naïves goes from 54 [30] to 56% [26], are even more ahead on the course. Adding AMA to combination regimens with standard IFNs is probably unsuccessful in naïves. In fact, an interim analysis at 26 weeks of induction therapy with daily, high-dose IFN-α-2a in combination with ribavirin and AMA in 168 naïves has not shown any increase of the response rate [31]. The issue of three-drug combination regimens could be more promising in non-responders to IFN or to IFN plus ribavirin. Brillanti recently published [20] a randomized controlled trial including 60 patients with chronic hepatitis C, non-responders to previous courses of IFN. Forty received IFN-α-2b at a dose of 5 MU on alternate days, ribavirin (800–1000 mg daily) and AMA (200 mg daily) for 12 months, and 20 had the same treatment without AMA. After 6 months of follow-up, 57 (23/40) and 10% (2/10) of patients treated with a triple or a double therapy had achieved SR. Conversely, Teuber and colleagues [32] have just reported negative results in a German multicentre study evaluating the efficacy of triple therapy vs. the IFN/ribavirin combination in 134 IFN non-responders. IFN was given as the induction at 5 MU daily for the first 4 weeks, followed by 5 MU t.i.w. for 20 weeks, and then 3 MU t.i.w. for 24 weeks. The SR rates were not significantly higher in patients receiving triple therapy than in those on IFN/ribavirin (23.4 vs. 17.1%). Other studies of triple therapy with or without IFN induction [33–36] in smaller series of non-responders or relapsers to IFN monotherapy would suggest that adding AMA does not recover a significant amount of sustained responsiveness. It is unknown whether the slight advantage observed for AMA in viral clearance rates at 3 months in naïves [27,28] also exists in non-responders.

Again, it is difficult to explain why these studies differ in their conclusions. Besides intrinsic differences in the schedules and in the selection of patients, it should be reminded that the definition of non-response to IFN monotherapy is not as clear-cut as that of response: 'partial responders' and breakthrough patients, who are intrinsically interferon sensitive, may have been included at different rates in these trials. Moreover, it would be relevant now to know if AMA helps to re-treat non-responders to IFN/ribavirin, who are likely to be much tougher clients.

If pegylated IFNs (PEG) are going to be the future standard, we need information on their combination with AMA. Data on the early kinetics of response to PEG + AMA have just been provided for naïve patients [37], for relapsers (Herrine et al., Digestive Disease Week, Atlanta, GA, 2001) and for non-responders (Afdahl et al., Digestive Disease Week, Atlanta, GA, 2001) to IFN/ribavirin. At 24 weeks, PEG + AMA had cleared HCV-RNA in 69% of naïve, in 32% of relapsers and in 18% of non-responder patients, while PEG + RIBA had induced clearance in 69% of relapsers and 30% of non-responders. Triple therapy (PEG + RIBA + AMA) was apparently more effective, obtaining negativization of HCV-RNA in 81% of relapsers and 39% of non-responder patients. Thus, in proportion to the patient's sensitivity to IFN, AMA seems to enhance the effects of the combination of PEG and ribavirin, albeit being scarcely effective by itself.

Finally, some more question marks remain. First of all, even if most randomized studies have essentially negative results in terms of SR, most show a non-significant trend favouring AMA. The study sample size may be inadequate to exclude a type β (false negative) error. Pooling of individual patient data among some of these trials is underway in order to perform a meta-analysis to conclusively solve this issue. All trials have used a fixed dose of AMA, which was seemingly derived from its use in neurology rather than from any evidence of antiviral activity. Dose-finding trials could be useful in exploring the possibility of underdosing, which theoretically could have affected the effectiveness of the drug in trials performed in populations with a higher mean body mass index. The HCV replicon model could also be helpful in sorting out in vitro the right amount of drug. The formulation of AMA used could be relevant: all studies reporting some positive results have used AMA hydrochloride, while the negative German trials were performed with AMA sulphate. Are the bioavailability, pharmacokinetic and pharmacodynamic properties of AMA hydrochloride and sulphate equivalent? And, on the same line, is the much less exploited RIMA equivalent to AMA?

To sum up, this low-cost and highly tolerable drug has somehow defeated its initial promises of efficacy against HCV. Part of the disappointment may be due to the relatively high level of efficacy reached by the current combination schedule. Given the current shortage of promising alternatives, before giving up AMA, it would be wise to re-explore its clinical potential in combination with pegylated IFNs and ribavirin in non-responders, using cohorts of patients sufficiently large to analyze predictors of effectiveness. The search for better antiviral drugs is still on!

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