Abstract. Ribavirin is a nucleoside analogue with antiviral activity against a number of DNA and RNA viruses. That molecule is administered per os and its most frequent adverse effect is haemolysis, moderate in most cases. Used alone, ribavirin normalized liver enzyme concentrations in 45% of patients while viraemia is not significantly modified. Histological improvement is observed in responder patients. The most interesting results have been obtained by associating ribavirin with interferon. In patients who have never been treated, a six-month course of ribavirin–interferon association produced a lasting and total response in 47% of patients versus 25% in patients treated with interferon alone. In relapsers, this bi-therapy produced total and prolonged response in more than 40% of cases and in 20% of non-responder patients. Lastly, that association appears promising in treating hepatitis C reinfection after liver transplantation.

Introduction

In the absence of animal (apart from chimpanzees) or cellular models to study human HCV chronic infection, research for active molecules against this virus has been difficult.

Considering the known effectiveness of ribavirin against a wide range of RNA or DNA viruses and particularly against flaviviruses, it was only logical to use this drug in HCV infection. This paper therefore mainly focuses on the interest of that molecule in monotherapy or in association with interferon.

Properties of ribavirin

Ribavirin is a synthetic nucleoside analogue. Viruses sensitive to that compound are Influenza A and B, HAV, HBV, Lhassa fever, measles, and herpes simplex. The molecule is essentially used in the form of spray to treat respiratory syncytial viral pneumonia in children [1].

The mechanism of action of Ribavirin is little known. It is certainly complex, involving: (i) inhibition of RNA-dependent polymerase RNA; and (ii) depletion of the guanosine-triphosphate intracellular pool indirectly responsible for obliterating viral nucleic acid synthesis through the inhibition of inosine monophosphate dehydrogenase, and potentially abnormal RNA synthesis.

Ribavirin is rapidly absorbed with a bio-availability of 33–69% in man; after oral administration, the serum concentration peak ($C_{\text{max}}$) occurs rapidly, in 1–2 h and is delayed in cases of hepato-cellular failure. Pharmacokinetics appear to be linear, from 600 to 2400 mg. The serum peak after a single oral dose of 600 mg is 3–5 mmol. Ribavirin is widely distributed in all parts of the organism, including red blood cells and the cerebrospinal fluid (CSF). The red blood cells rapidly capture the molecule and whole blood concentrations remain high long after the molecule has disappeared from the serum (or plasma).

Plasma half-life varies from 18 to 160 h in the absence of renal failure. Excretion is urinary and renal elimination is reduced three folds in case of creatinine clearance of 20–30 ml/min. Stable plasma concentration is achieved in 4 weeks with a daily dose of 600 mg.

Ribavirin tolerance is globally good beside slight haemolysis secondary to accumulation in erythrocytes. It can involve 5–10% of RBC.

Effectiveness of ribavirin as monotherapy

Open pilot studies

Two initially non-controlled studies have been reported. The first study was with a total daily dose of 1 g or 1200 mg (depending on body weight being below or above 70 kg) in two daily intakes for 4 months, and was conducted in Sweden by Reichard [2]. The other study, by Dibisceglie at the NIH [3], involved administration of ribavirin for 6 months in stepped-up doses from 600 to 1200 mg every 2 months. In both studies, transaminases decreased in nearly all patients during treatment but they increased again at the end of ribavirin treatment in all patients but one. Although a decrease in HCV RNA was observed, it was only transient and in all cases viraemia persisted and returned to its initial level after the end of treatment.
**Controlled studies**

Three controlled studies have since been conducted. They included 59 assessable patients including 15 men and 44 women aged 23–69 years, mean age 44 years. Each of these three studies gave positive results in transaminase normalization, as observed in 45.7% of treated patients vs 4% of control patients.

Viraemia was eradicated in 3–10% of cases but that difference was not significant relatively to the control group. Histologically, the benefit observed after meta-analysing the three studies was particularly clear-cut. Comparisons were made between responder patients (improved transaminases) and non-responders. A 55% improvement and 37% stabilization were observed in the former, vs 40% and 22% in the latter, respectively.

In a short 4–6-month course, ribavirin demonstrated, by these controlled trials, its beneficial effect on transaminase, associated with a positive histological effect on responders, without any significant reduction of viraemia. Interestingly, response factors appeared to differ from those known for interferon. The severity of histological lesions in these three studies did not appear to be a clear factor of poor response or of previous interferon therapy. The percentage of responders was not significantly different in patients infected with strain 1b (54%) relative to strain 2 (57%).

More extended trials were conducted at the NIH in 27 patients. There was total response in 15%, partial response in 37%, and only 37% had no response at all. Treatment had to be suspended and doses reduced in 10% of patients. In responder patients, Knodell’s score decreased from 11.5 to 7.7 whereas it remained unchanged in non-responders (11.8–11.5).

In six responder patients treated for 2 years, histological improvement was maintained in the second year and Knodell’s score improved by 50% with regard to the initial pre-treatment figure. Although there was no withdrawal, even in these patients treated for more than one year, no significant variation could be documented in terms of quantitative viraemia. But some patients who remained viraemic kept exhibiting normal transaminase values for a long time after stopping the prolonged treatment.

**Ribavirin–interferon association**

Four controlled studies are available although only one has been published in full. The other ones were either oral communications or abstracts. Several studies are under way and others in preparation. All these trials lead to distinguishing between three types of situations: patients who have never been treated, relapsers and initially non-responding patients.

All the protocols compared patients receiving interferon alone in classic doses with a group of patients treated with the same dose of interferon 3 MU for 6 months in association with 800–1200 mg ribavirin.

With the patients who had never been treated in Chemello’s study [6], the response rate at the end of 6-month treatment course was 73% in the group receiving interferon alone or in association with ribavirin, and 40% with ribavirin alone. In contrast, 6 months after treatment, all patients who had received ribavirin alone relapsed whereas 47% who had bi-therapy remained in complete remission, versus 27% in patients receiving interferon alone. The full remission, when achieved by bi-therapy, persisted for one year after the end of treatment, whereas a number of patients treated with interferon alone relapsed. Virologically, full biological and virological remission was not observed in any patient treated with ribavirin alone but was observed in 13% of patients treated with interferon alone, and in 47% of patients treated with the ribavirin–interferon. Patients with cirrhosis responded less often to bi-therapy (20%) than those with no cirrhosis (60%).

In relapsers, who already fully responded to a first treatment course, lasting and full response to bi-therapy was obtained in more than 40%, in sharp contrast with the 20% observed with a new course of the same dose of interferon alone.

In non responders or partial responders, according to several studies, bi-therapy is likely to provide substantial benefit and lasting full remissions in the order of 20%.

The excellent concordance between different studies [6–8] conducted in very different populations of very different patients in Europe and worldwide is an extremely convincing factor in favour of interferon-ribavirin association, which appears to be truly synergistic.

This has also been fully confirmed by the results observed with the interferon–ribavirin association in liver transplantation.

**Ribavirin–interferon association in treating graft re-infection following liver transplantation**

Classically, the results of interferon therapy in transplantation have been disappointing. But viral re-infection is a constant occurrence and there is currently no effective prevention. Fifty per cent of reinfected patients develop active chronic hepatitis with a risk of cirrhosis and re-transplantation in 20% of cases. The severity of that re-infection is linked to the increased viral titre and to genotype 1b, among other factors. In spite of these major handicaps, during early treatment with the ribavirin–interferon association followed by ribavirin alone as a maintenance treatment [9], transaminase concentrations are durably normalized in all patients treated for more than 1 year, with histological improvement in 85% of cases and virological benefit confirmed by viral quantification, and with no rejection!

The effectiveness of bi-therapy in such a situation, which is the most pejorative of all, is the best justification for the hopes and expectations put in that association.
References