Editorial – Hepatitis C

Professor Graham Foster
Professor of Hepatology
Queen Mary's School of Medicine, London

Interferons were discovered almost 50 years ago when Isaacs and Lindenman noticed that extracts from cells exposed to influenza had antiviral properties. Initially developed as anticancer drugs, the antiviral properties of the interferons were exploited in the 1980s when they were used in the therapy of patients with chronic hepatitis B. Since then, interferons have been studied in a number of different viral disorders, but their main clinical application is in the therapy of patients with chronic hepatitis C.

Hepatitis C was unknown at the time of the discovery of the interferons and, indeed, was originally identified as a viral infection that was not hepatitis A or hepatitis B (or non-A non-B hepatitis). Molecular identification of the virus in the late 1980s allowed it to be characterised, and it was subsequently renamed as hepatitis C.

Early studies in patients with chronic hepatitis C showed that therapy with interferon was beneficial and a large proportion of patients had a biochemical response with improvement in their liver function tests. Sadly, subsequent studies showed that many such patients did not eliminate the virus and soon relapsed leading to the recognition that interferon monotherapy benefited only a few patients. However, when interferon was combined with the weak antiviral agent ribavirin, a remarkable synergy was observed with up to 40% of patients achieving a sustained virological response.

Early clinical trials with interferon and ribavirin showed that many patients had severe side-effects that resulted in premature discontinuation of therapy. Therefore, attempts were made to improve the tolerability and efficacy of the therapy, with efforts focused on the pharmacology of the interferon. Unmodified interferon has a very short half-life which necessitates thrice-weekly dosing and reduces antiviral efficacy and accentuates the side-effects that are associated with fluctuating drug levels. To improve the half-life of interferon, the native molecule was linked to inert polyethylene glycol (PEG). This 'pegylated interferon' was shown to have a much longer half-life compared with the unmodified interferon.

Clinical trials with the 40 kDa pegylated interferon alfa-2a have demonstrated that the hopes for a more efficacious drug with fewer side-effects have been realised. Thus, both in monotherapy and in combination with ribavirin, the 40 kDa pegylated interferon is significantly more effective than standard interferon, with the side-effects also being less pronounced with the pegylated drug. Of great importance to clinicians and their patients, these benefits are seen in all patients with chronic hepatitis C whilst all of the different viral genotypes benefit from therapy with this drug. Recent studies in the most refractory patients with hepatitis C, including African-Americans and patients coinfected with HIV, show that the 40 kDa pegylated interferon alfa-2a is also effective at allowing more patients with chronic hepatitis C to benefit from therapy.

As we approach the fiftieth anniversary of the discovery of the type I interferons it is interesting to reflect that their major clinical use is in the therapy of a viral infection that was unknown at the time of their discovery! Sophisticated modification of the pharmacodynamic properties of the basic interferon has led to the development of a drug that is both more effective and better tolerated than the original version. After nearly 50 years of experience with the interferons, it is true to say that the pegylated interferon molecule has finally come of age.

Drugs in Context
DOI:
http://dx.doi.org/10.7573/dic.212201

Citation: Foster, G. Editorial – Hepatitis C. *Drugs in Context*: e212201. doi:10.7573/dic.212201