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for chronic hepatitis generally (Table 3.1), and it has an acceptable performance in biopsies of HCV liver disease (Westin *et al.* 1999).

**Table 3.1** The definitions of the Ishak scoring system

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*A: Periportal or periseptal interface hepatitis (piecemeal necrosis)*

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- 0: Absent
  - 1: Mild (focal, few portal areas)
  - 2: Mild/moderate (focal, most areas)
  - 3: Moderate (continuous, <50% of tracts)
  - 4: Severe (continuous, >50% of tracts)
- 

*B: Confluent necrosis*

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- 0: Absent
  - 1: Focal confluent necrosis
  - 2: Zone 3 necrosis in some areas
  - 3: Zone 3 necrosis in most areas
  - 4: Zone 3 necrosis + occasional P-C bridging
  - 5: Zone 3 necrosis + multiple P-C bridging
  - 6: Panacinar or multiacinar necrosis
- 

*C: Focal (spotty) lytic necrosis, apoptosis and focal inflammation.*

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- 0: Absent
  - 1: Mild (one focus or less /x 10 field)
  - 2: Mild/moderate (2–4 foci/x 10 field)
  - 3: Moderate (5–10 foci/x 10 field)
  - 4: Severe (>10 foci /x 10 field)
- 

*D: Portal inflammation*

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- 0: None
  - 1: Mild, some or all portal areas
  - 2: Moderate, some or all portal areas
  - 3: Moderate/marked, all portal areas
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*S: Staging*

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- 0: No fibrosis
  - 1: Some tracts expanded, ± septa
  - 2: Most tracts expanded, ± septa
  - 3: Most tracts expanded, ± P-P bridging
  - 4: Marked bridging, P-P and P-C
  - 5: Marked bridging, occasional nodules (incomplete cirrhosis)
  - 6: Cirrhosis, probable or definite
-

# Therapy with pegylated interferons

*GR Foster*

## Introduction

Chronic infection with the hepatitis C virus (HCV) is common in the United Kingdom (Sallie *et al.* 1994) and, without therapy, many of those who are infected will develop significant liver disease over several decades (Poynard *et al.* 1997). Current therapy for patients with chronic hepatitis C involves combination therapy with interferon- $\alpha$  plus ribavirin (Poynard *et al.* 1998; McHutchinson *et al.* 1998; Davis *et al.* 1998). In this regimen recombinant interferon  $\alpha$ -2 (IFN  $\alpha$ ) is given by subcutaneous injection three times per week in combination with oral ribavirin administered every day at a dose of 1200 mg daily (reduced to 1000 mg for patients weighing less than 75 kg). Although this therapy is effective and cures over 40% of those treated, it is unpleasant (up to 20% of patients discontinue therapy because of side effects (Foster 1999)) and relatively expensive. The combination of poor efficacy and poor tolerability has led to recommendations that this therapy be reserved for patients with biopsy proven severe disease and current guidelines (National Institute for Clinical Excellence 2000) recommend that all patients should undergo liver biopsy and only those with evidence of significant fibrosis should go on to receive therapy.

The relatively low efficacy of current treatment regimens has led to attempts to improve the potency and tolerability of therapy for hepatitis C. Several groups have attempted to develop modified ribavirins that lack the toxicity associated with this drug but, so far, no modified ribavirins have been shown to be effective. The main side-effect of ribavirin therapy is haemolysis leading to anaemia (Foster 1999) which may be significant and which adds to the unpleasant fatigue associated with IFN  $\alpha$  treatments (Fattovich *et al.* 1996). Attempts to identify non-haemolytic variants of ribavirin have, so far, been unsuccessful although the search for alternatives continues. Attention has therefore turned to the interferons to determine whether improvements in the half-life of this drug can be used to improve efficacy.

IFN  $\alpha$  is a low molecular weight protein that has antiviral and immunomodulatory effects (Pestka *et al.* 1987). The natural protein is rapidly cleared by the kidneys and the drug therefore has a very short half life such that during the usual thrice-weekly dosing regimen the serum concentration of IFN  $\alpha$  varies markedly. This large variation in serum concentration may enable resistant viral strains to emerge, thereby encouraging treatment failure; anecdotal evidence suggests that the rapid changes in

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