On the outcome of antiviral therapy for hepatitis C virus genotype 2 or 3 infection

Akademisk avhandling

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Avhandlingen baseras på följande delarbeten

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Abstract

Approximately 80% of patients infected with HCV genotypes 2 or 3 achieve a sustained virological response (SVR), following 24 weeks of therapy with ribavirin and pegylated interferon (peg-IFN), but in light of considerable side effects and cost, shortened treatment duration without impaired efficacy is desirable. Thus, 382 genotype 2/3 infected patients were randomized in an investigator-initiated phase III study (NORDynamIC) evaluating the efficacy of 12 (short-term) vs. 24 (standard-of-care) weeks of treatment with peg-IFN α-2a 180 µg/week and ribavirin 800 mg/day. Overall, 12 weeks of therapy was inferior to 24 (SVR 59% vs. 78%, P<0.0001) regardless of fibrosis stage or HCV genotype. However, in a multivariate intention-to-treat analysis, HCV RNA <1,000 IU/mL on day 7, age <40 years, and undetectable HCV RNA on day 29 were independent predictors of SVR following 12 weeks of therapy. Outcome of short-term treatment was similar to standard treatment in patients younger than 40 years, as well as in older patients provided that HCV RNA was <1,000 IU/mL on day 7 and undetectable on day 29. Patients achieving HCV core antigen (coreAg) levels in plasma <0.2 pg/mL on day 3 had similar sustained viral response (SVR) rates in both study arms (86% and 84% for 12 vs. 24 week arms respectively). Patients who never achieved undetectable HCV RNA (n=12), had significantly higher age, pretreatment viral load, and body mass index (BMI) as well as lower interferon concentrations on days 7 and 29. Similarly, obesity (BMI ≥30 kg/m²) was significantly associated with lower peg-IFN and ribavirin concentrations which entailed impaired outcome following 24 weeks of therapy (SVR 62% vs. 89% for BMI ≥30 vs. <30; P=0.006). In a multivariate analysis among per-protocol patients in the 24 week arm, ribavirin and peg-IFN concentrations, as well as baseline HCV RNA levels were independent predictors of SVR, suggesting that reduced bioavailability of interferon and ribavirin in obese patients may affect treatment outcome. Pretreatment plasma levels of Interferon-γ Inducible Protein 10 kDa (IP-10) predicted the reduction of HCV RNA during day 1-3 (first phase) but not the decline between days 8-29 (second phase). In addition, a significant association was identified between expression of intrahepatic IP-10 mRNA and plasma IP-10, indicating that the liver is likely the primary source of systemic IP-10 in chronic HCV infection.

Keywords: Hepatitis C, Treatment, Genotype, BMI, Drug concentration, IP-10