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ORIGINAL ARTICLE

Efficacy and safety of peginterferon plus ribavirin for patients aged ≥ 65 years with chronic hepatitis C: A systematic review and meta-analysis



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Summary

Methods: Studies up to August 30, 2012 of the efficacy and safety of peginterferon plus ribavirin therapy in CHC patients aged ≥ 65 years were systematically identified in PubMed, Ovid, Web of Knowledge and Cochrane Library databases. A meta-analysis was performed using both fixed- and random-effects models based on heterogeneity across studies.

Results: The overall sustained virological response (SVR) in CHC patients aged ≥ 65 years was significantly lower than in patients aged < 65 years on both intention-to-treat (ITT; 42.0% vs. 60.1%, respectively; $P < 0.00001$) and per-protocol (PP; 54.4% vs. 67.4%, respectively; $P = 0.002$) analyses, including treatment-naïve patients. Subgroup analysis showed that patients ≥ 65 years with either hepatitis C virus (HCV) genotype 1/4 or 2/3 had lower SVR rates than younger patients. No statistically significant differences were observed between the two groups in terms of rapid virological response (RVR) and early virological response (EVR) rates (both $P \geq 0.05$). However, the end-of-treatment virological response (ETR) rate was lower in patients ≥ 65 years, who also had a significantly higher risk of relapse than those aged < 65 years (39.8% vs. 26.9%, respectively; $P < 0.00001$). The discontinuation rate in the older patients was also significantly higher than in the younger patients (25.5% vs. 14.8%, respectively; $P < 0.00001$). Ribavirin dose reduction in the older patients treated with peginterferon plus ribavirin was also significantly higher than in younger patients (44.5% vs. 32.8%, respectively; $P < 0.00001$).

Abbreviations: CHC, chronic hepatitis C; SVR, sustained virological response; RVR, rapid virological response; EVR, early virological response; ETR, end-of-treatment virological response; HCV, hepatitis C virus; CI, confidence interval; ITT, intention-to-treat; PP, per-protocol; NRCCTs, non-randomized concurrent controlled trials.

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Conclusion: Peginterferon plus ribavirin therapy was effective for older patients with CHC, particularly those with HCV genotype 2/3. Response-guided therapy can be used for older patients with genotype 1/4, but such patients had poorer treatment adherence, leading to poorer treatment efficacy.

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Background

The World Health Organization (WHO) estimates that as many as 170 million people worldwide (approximately 3% of the world's population) may be infected with the hepatitis C virus (HCV). The disease is responsible for approximately 350,000 deaths every year. The virus is spontaneously cleared in only about 20% of cases, and chronic infection frequently progresses to cirrhosis, end-stage liver disease, hepatocellular carcinoma (HCC) and death [1–4]. Chronic HCV infection is characterized by an increased prevalence with aging, particularly in industrialized countries such as Japan and Italy [5,6]. In Taiwan, the age at which the anti-HCV seroprevalence rate is at its peak is 60–80 years [7]. In the US, a survey found an anti-HCV prevalence of 0.9% in those ≥ 60 years of age [8]. Previous studies have also shown that the rate of cirrhosis development is higher in older CHC patients. In addition, the prevalence of cirrhosis becomes more frequent with age [9,10].

Antiviral treatments for CHC have significantly improved over the past few decades. Although triple therapy is now recommended in Northern countries for CHC patients with HCV genotype 1, in many countries the first-line therapy currently recommended for CHC is still a combination of peginterferon α and ribavirin in accordance with the current guidelines [1,2]. However, data on the efficacy and tolerability of peginterferon plus ribavirin antiviral therapy in elderly CHC patients are limited, which means that elderly patients are seldom treated with the combination therapy. In a prospective cohort study reported by Tsui et al. [11], 9% of 4025 patients screened throughout the US were elderly, and 25% of these elderly patients were considered possible treatment candidates by their evaluating clinician, yet only 10% were started on treatment. Indeed, after adjusting for comorbidities, old age remained associated with a lower likelihood of being a treatment candidate [12]. There are three possible explanations for this:

- randomized controlled trials generally exclude patients aged ≥ 65 years;
- little data are available on the beneficial effects of peginterferon plus ribavirin therapy for long-term outcomes in elderly patients;
- the high risk of possible adverse events may account for the lower treatment rate in elderly CHC patients.

Nevertheless, it is precisely this category of patients that commonly requires aggressive treatment because of the high risk of disease progression [10,13,14]. Yet, the efficacy and safety of peginterferon plus ribavirin therapy in CHC patients aged ≥ 65 years remains controversial [10,15–24]. For this reason, a systematic review of these small-sample studies is

essential to gain further insight into the effects of antiviral therapy in this specific population.

Methods

Search strategy

PubMed, Ovid, Web of Knowledge and Cochrane Library databases were searched for studies published up to August 30, 2012. The following medical subject headings (MeSH) were used: 'Hepatitis C, chronic', 'interferons', 'ribavirin' and 'aged'. Supplemental searches of reference lists of all retrieved review articles and primary studies were also conducted to identify other studies not found by the initial electronic searches. The literature was independently searched by two of the present authors (Z.G. Yang and L.P. Zhuang).

Study selection

The two authors independently selected the trials for analysis and arrived at a consensus when discrepancies arose. Studies were included only if they met the following criteria:

- the study was a non-randomized concurrent controlled trial (NRCCT), whether prospective or retrospective;
- patients had CHC and were divided into at least two groups according to age, including those ≥ 65 years;
- patients in the different age groups were all under the same treatment protocol – namely, peginterferon plus ribavirin;
- the studies used one or more of the following outcome measures: rapid virological response (RVR); early virological response (EVR); end-of-treatment virological response (ETR); sustained virological response (SVR); discontinuation rate; and relapse rate;
- full texts of the studies were available.

Reports with the following characteristics were excluded:

- follow-up period of < 6 months;
- study patients had liver diseases other than HCV such as hepatitis B virus infection, immunodeficiency virus infection and HCC.

Methodological quality-assessment

To assess the methodological quality of the NRCCTs, the Methodological Index for Non-Randomized Studies (MINORS) guidelines [25] were used. These guidelines list 12 indices for comparative studies:

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