Treatment of chronic hepatitis C in polytransfused thalassaemic patients: a meta-analysis

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CRD summary
This review assessed the effect of current anti-hepatitis C virus (HCV) treatment in polytransfused thalassaemic patients and concluded that patients infected with Genotype 1 HCV benefited from addition of ribavirin to their therapeutic regimen; although it may increase transfusion need, it did not increase adverse event rates. For methodological reasons the validity of this conclusion is unclear.

Authors' objectives
To analyse the effect of current anti-hepatitis C virus (HCV) treatment in polytransfused thalassaemic patients.

Searching
MEDLINE, SCOPUS, Web of Knowledge and Cochrane Central Registry of Clinical Trials (CENTRAL) were searched for relevant articles. Search terms were reported. No date restrictions were applied. Bibliographies of all retrieved records and reviews were searched for further relevant studies.

Study selection
Studies were eligible for inclusion if: the study used a single prospective arm or controlled design and involved more than 10 patients; patients were thalassaemic patients with polymerase chain reaction (PCR) detectable HCV RNA (ribonucleic acid); the therapy was PEGylated or conventional interferon alpha in or not in combination with ribavirin; papers reported the sustained virological response (SVR), defined as negative PCR beyond six months treatment, and stated the rate of drop-out and withdrawal. Studies were excluded if patients were co-infected with human immunodeficiency virus (HIV) or hepatitis B virus (HBV) or received bone marrow transplantation or immune suppressive agents.

Most of the included studies used a prospective cohort design; one was a non-randomised clinical trial and two were randomised clinical trials. The percentage of male patients ranged from 38% to 75%. Studies were conducted in a range of countries. Average age of participants ranged from 13 to 27 years. The average stage of fibrosis ranged from 1.5 to 3.7. Interferon total doses ranged from 216 to 8,640 units (unit not defined). Most studies used monotherapy rather than combination therapy and used either the IFNα2a or IFNα2b (conventional interferon α) protocol; others used either the PEGα2a or PEGα2b (PEGylated interferon α) protocol; combination therapies mostly used RVB (ribavirin).

The authors did not state how many reviewers performed the study selection.

Assessment of study quality
All studies needed to report withdrawal and drop-out rate as part of the study selection. RCTs were assigned a quality score, but no further details were reported.

The authors did not state how many reviewers performed the validity assessment.

Data extraction
The reviewers extracted data required to calculate the sustained virological response (SVR) defined as undetectable HCV-RNA in blood using PCR techniques at least six months after the end of treatment. The review extracted side effects data and reasons given for discontinued treatment.

It appeared that one reviewer extracted data, which was then checked twice.

Methods of synthesis
The reviewers pooled SVRs from different studies using random-effects and fixed-effect models. Heterogeneity was
assessed using the Q-test (p<0.10 indicated significant heterogeneity) and I² statistics.

Various subgroup analyses were performed. These included odds ratios (ORs) (calculated using the fixed-effect method) that compared SVR in two types of HVC (genotype 1 and non-genotype 1), differences in SVR in responders and non-responders, differences in SVR in monotherapy compared with combination therapy and differences in SVR between patients given different types of IFN therapy.

The review did not state how many authors performed the synthesis.

**Results of the review**

Sixteen studies were included in the review (n=546 patients, range 10 to 89 patients): one randomised controlled trial, two clinical controlled trials and 13 prospective cohort studies. Thirteen of the 16 studies were included in the meta-analyses. The withdrawal and drop-out rate ranged from 0% to 47%.

Overall pooled SVR rate was 44.7% (95% CI 34.6% to 54.9%) with a random-effects model and 40.3% (95% CI 36% to 44.6%) with a fixed-effect model (n not stated clearly). Heterogeneity was significant (I²=79.6%).

Subgroup analyses indicated no significant differences in SVR between genotype 1 and non-genotype 1 infected patients, except in patients treated with IFN monotherapy where SVR was lower in genotype 1 infected patients (pooled OR 0.46, 95% CI 0.22 to 0.95). Genotype 1 patients who received standard IFN monotherapy (n=66 patients, three trials) had a lower SVR (29.5%, 95% CI 18.7 to 40.4%, I²=0%) than those treated with a combination of standard IFN plus ribavirin (pooled SVR 60.9%, 95% CI 32.4 to 89.4%, I²=53.3%; two trials, n=31 patients). SVRs for other subgroups were reported.

Side effects reported included granulocytopenia, fever, fatigue, anorexia, weight loss, headache, myalgia, arthralgia, neutropenia, thrombocytopenia, hyperhaemolysis, anaemia, oedema and alopecia. More common reasons given for discontinuing treatment included increase transfusion rate and death; more details were provided in the review.

**Authors’ conclusions**

Thalassaemic patients with Genotype 1 infection benefited significantly from the addition of ribavirin to their therapeutic regimen; although use of ribavirin may increase transfusion need by around 30% to 40%, it did not increase the risk of major adverse events and treatment withdrawal.

**CRD commentary**

This review addressed a clear research question with clear and appropriate study selection criteria. A number of databases were searched. Search terms were reported. Measures were taken to identify further relevant studies. The review did not state whether language restrictions were reported, so the possibility of language bias could not be ruled out. Sufficient primary study details were reported, which improved review transparency. The validity assessment appeared appropriate, but was not reported fully as only aggregate quality scores were provided. It was unclear whether the data extraction and most other stages of the review process were conducted by more than one reviewer; if they were then the risk of reviewer error and bias was reduced. The method of synthesis appeared broadly appropriate, subject to three caveats: treatment comparisons with control groups were not reported and perhaps not conducted, so the added benefit of any of the active treatments was uncertain; the use of many subgroup comparisons made the analysis more likely to identify spurious associations by chance; and large and long-term observational studies may have been needed to identify rare but serious adverse events.

The conclusion focused on a subgroup of patients treated with a subgroup of the treatment types, and made a claim about two treatment types having equivalent adverse event profiles; it may not be reliable for the reasons stated.

**Implications of the review for practice and research**

Research: The authors stated a need for more evidence about use of PEGylated interferon as monotherapy or in combination with ribavirin in thalassaemic patients.
Practice: The authors did not state any implications for practice

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