Recombinant human hepatocyte growth factor for liver failure


CRD summary
This review concluded that recombinant human hepatocyte growth factor (rhHGF) plus comprehensive therapy may reduce mortality in liver failure patients compared to comprehensive therapy alone. The authors' conclusions are reasonable given the evidence presented, but the generalisability of this review was unclear and clinical significance uncertain in view of the poor quality of included trials.

Authors' objectives
To evaluate the efficacy and safety of recombinant human hepatocyte growth factor (rhHGF) for liver failure.

Searching
Published trials were identified through a search of PUBMED, EMBASE, Chinese Biomedical Database (CBMdisk), CNKI, Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews to 2007. Handsearching was undertaken. Search terms were reported.

Study selection
Randomised or quasi-randomised trials of rhHGF plus comprehensive therapy compared with comprehensive therapy alone in patients with liver failure were eligible for inclusion. Patients were eligible for inclusion regardless of the cause of liver failure, age, gender or ethnic origin. The primary outcome was mortality. Secondary outcomes included mortality related to the type of liver failure, mortality related to stage of liver failure and adverse events.

Viral infection was the cause of liver failure in all included trials. For most trials, rhHGF was administered intravenously at 80mg to 120mg in 10% glucose once a day for 30 days. Comprehensive therapy routinely included amino acids, blood products, glucagons-insulin and thymosin. Most trials provided therapy for four weeks (range two to eight weeks).

Two reviewers independently selected studies for inclusion. Disagreements were resolved through discussion.

Assessment of study quality
The quality of studies was assessed using Cochrane Collaboration methodology, specifically the criteria of randomisation, allocation concealment, blinding, withdrawals and drop outs. Studies were then assigned grades from A (adequate with correct procedures) to C (inadequate procedures, methods or information). The authors did not state how the validity assessment was performed.

Data extraction
Data on numbers of events in each group were used to derive risk ratios (RR) and 95% confidence intervals (CI) for dichotomous outcomes. Two reviewers independently extracted data; disagreements were resolved by discussion. Where missing data were observed, study authors were contacted.

Methods of synthesis
The pooled RR and corresponding 95% CIs were calculated using a fixed-effect meta-analysis where there was no evidence of statistical heterogeneity. A random-effects model was used if statistically significant heterogeneity was observed. Analyses were conducted by intention-to-treat where possible. Statistical heterogeneity was assessed using a X² test. Subgroup analysis investigated the effects of different clinical types of liver failure (acute, sub-acute and acute-on-chronic) and stages of liver failure (early, middle and late). Sensitivity analyses were conducted to test the influence of randomisation condition and trial size. Publication bias was assessed using Begg and Mazumdar adjusted rank correlation test and funnel plots.

Results of the review
Twenty one trials (n=5,902) were included in the review. Overall study quality was poor: one trial scored B; most scored C.

rhHGF plus comprehensive therapy reduced overall mortality compared with comprehensive therapy alone (RR 0.62, 95% CI: 0.59 to 0.66; 21 trials). Subgroup analysis according to randomisation condition (randomised and quasi-randomised) and sensitivity analyses excluding the two largest trials did not alter results. No significant heterogeneity was observed for any outcome.

In terms of clinical type of liver failure rhHGF plus comprehensive therapy significantly reduced mortality in patients with all types of liver failure compared with comprehensive therapy alone, although there was a greater reduction reported for sub-acute liver failure (RR 0.58, 95% CI: 0.53 to 0.64; 12 trials) compared to acute liver failure (RR 0.76, 95% CI: 0.65 to 0.89; 10 trials) and acute-on-chronic liver failure (RR 0.66, 95% CI: 0.60 to 0.74; 11 trials).

In terms of clinical stage of liver failure, rhHGF plus comprehensive therapy significantly reduced mortality in patients at all stages compared with comprehensive therapy alone, with a greater reduction reported for early stage (RR 0.34, 95% CI: 0.24 to 0.49; four trials) compared to middle stage (RR 0.49, 95% CI: 0.44 to 0.55; six trials) and later stage (RR 0.87, 95% CI: 0.82 to 0.93; six trials).

Adverse events were described in seven trials and were reported for 42 out of 5,902 patients (0.7%) treated with rhHGF plus comprehensive therapy. Adverse effects reported most often included skin rash, headache and low fever.

Publication bias was not observed.

Authors’ conclusions
Recombinant human hepatocyte growth factor plus comprehensive therapy may reduce mortality in liver failure, especially in sub-acute liver failure and early-stage liver failure, compared to comprehensive therapy alone. Considering the strength of the evidence, additional randomised controlled trials were needed before rhHGF plus comprehensive therapy can be recommended routinely.

CRD commentary
This review addressed a clear question supported by appropriate inclusion criteria. Relevant databases were searched, although language restrictions were unclear and there appeared to be no attempts to identify unpublished data. Suitable methods to minimise risk of reviewer error and bias were reported for study selection and data extraction, but not for validity assessment. Results were pooled using meta-analysis and heterogeneity was assessed. All included studies were undertaken in China, which probably limited the generalisability of this review. None of the included studies were considered to be high quality and most scored the lowest grade (C) on validity assessment, which made the results difficult to interpret.

This review was carried out robustly. The authors’ conclusions are reasonable given the evidence presented, but the generalisability of the review was unclear and clinical significance uncertain in view of the poor quality of included trials.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that future studies that evaluated the effectiveness of rhHGF were required and should be rigorously designed multicentre randomised double-blind controlled trials with large sample sizes.

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