Letters to the Editor

from ROCHE Austria. He is also member of the global advisory boards of Tibotec, Novartis/HGS and Rottapharm-Madaus.

Conflict of interest

All other authors have no financial disclosures to report.

References


Silibinin in hepatitis C related liver transplantation

Reply to Beinhardt et al.: We congratulate Beinhardt et al. for their interesting paper about successful prevention of hepatitis C virus (HCV) reinfec tion by short-term administration of high-dose silibinin infusions before and after OLT [1]. Preventing HCV reinfec tion has an enormous impact on the long term outcome of liver transplantation. Since interferon alpha based treatment regimens are not tolerated early after OLT and also in most instances in the pre-transplant setting, silibinin mono therapy seems to be a promising treatment option – supported by its reasonable safety profile, as documented by its use in amanita-induced acute liver failure.

Success or failure of preventing re-infection with a short term silibinin mono therapy seems to depend mainly on the level of hepatitis C viremia, usually seen during the anhepatic phase, works syner gistically with the direct antiviral effect of silibinin infusion to support the prevention of re-infection.

As an additional mode of action, a direct inhibitory effect of silymarin components towards the viral entry into hepatocytes has been proposed in vitro [2].

In both cases, in ours [3] and the one reported by Beinhardt et al. [1], HCV RNA levels were low at the time of OLT and particularly after the anhepatic phase (range of 10^2 IU/ml). The approach reported here includes a silibinin treatment before OLT, hereby significantly lowering viremia in order to provide beneficial conditions for the successful prevention of re-infection. This might significantly enlarge the pool of patients benefiting from post-OLT silibinin infusions. However, since the exact timing of the transplantation is usually not feasible, a standardization of the reported procedure seems to be difficult and is probably only possible in the setting of living donor liver transplantation (LDLT).

Up to now little is known about the safety of high dose sili binin infusions in the setting of end stage chronic liver disease. In our hands patients with advanced cirrhosis showed a marked elevation of bilirubin (mainly indirect) in response to silibinin infusions – an observation that was not seen in patients with mild or moderate fibrosis. The clinical significa nce of this bilirubin elevation remains unclear. At the same time this finding is obviously affecting MELD-score depending organ allocation.

Clearly the potential of silibinin infusions in the peri-trans plant period in HCV infected patients needs further evaluation. Studies should address several open questions as the optimal duration of treatment after OLT, the safety and effectiveness of silibinin infusions before OLT, and the potentially enhancing effect of adding ribavirin to silibinin infusions.

Conflict of interest

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

References


Anemia – The overlooked factor in bleeding related to liver disease

To the Editor:
Several elegant studies, summarised in their review by the Coagulation in Liver Disease Study Group, have helped in changing the paradigm of bleeding related to liver disease, from abnormal coagulation profile to haemostatic alterations secondary to portal hypertension, endogenous heparinoids, sepsis, and renal failure [1]. However, one of the key omissions in this respect is the role of anemia in worsening the haemorrhagic tendency of liver dysfunction. Anemia is common in individuals with chronic liver disease and is likely to be of multifactorial etiology including folate deficiency, hypersplenism, hemodilution, haemolysis, bone marrow suppression due to viruses or ethanol, renal insufficiency, and, most importantly, variceal bleeding. How anemia would worsen the bleeding tendency in these patients has not been directly studied but several factors are responsible.

Firstly, anemia worsens the hyperdynamic circulation, the key pathogenetic feature of portal hypertension [2]. This is possibly due to the reduction in blood viscosity but some evidence for the role of the vasodilator nitric oxide (NO) has also been suggested [3]. As demonstrated in experimental animals, NO may also play a central role in the systemic and splanchic vasodilatation associated with portal hypertension with increased vascular responses to specific inhibitors of NO biosynthesis [2]. Secondly, there is evidence that red blood cells not only have passive, rheological effects on blood coagulation but also actively stimulate thrombin generation [4]. The best example of the haemostatic role of red cells is represented by the increased thrombotic tendency of polycythemia and erythropoiesis-stimulating agents. Interestingly, a small prospective study of 42 patients with chronic anemia (unrelated to liver disease) showed an unexplained improvement in the activated partial thromboplastin time with increased vascular responses to specific inhibitors of NO biosynthesis [2].

By far, the most likely explanation for the bleeding tendency with anemia is the effect of red cells on platelet function. Red cells release adenosine diphosphate which promotes platelet aggregation and also stimulates platelet synthesis of thromboxane A2, a key platelet activator during vessel injury. Haemoglobin could also play an important role because of its high affinity for NO. The reduced NO scavenging, caused by the reduced level of haemoglobin in anemia, activates guanylyl cyclase and further impairs platelet aggregation. Moreover, in normal physiological states, red cells, being the largest cells, tend to occupy the central part of the vasculature, pushing the platelets nearer to the vessel wall, where they are poised to respond to injury. In anemic states, the concentration of platelets in proximity to the endothelium is reduced thus affecting the haemostatic process. The beneficial effect of red cells on platelet function was first reported by Duke in 1910 but was conclusively proved by Hellem who examined anemic patients with bleeding defects showing a decrease in bleeding time (BT) upon transfusion of washed red cells [6]. This observation has been more recently confirmed, when improved BT after red cell transfusions were observed in experimental and clinical subjects with continued thrombocytopenia and in uremic patients with bleeding tendency and normal platelet counts [7,8]. One of the possible negative arguments for these studies would be the assessment of BT rather than further bleeding episodes, with red cell replacement. BT is prolonged in cirrhosis to variable extent, although the exact cause for this phenomenon has never been explained, especially when there was no negative correlation between platelet counts and BT, and an abnormal VonWillebrand factor was not seen in these patients [9]. In this context, it is useful to remember that BT is not just a measure of platelet function but is also influenced by red cell volume, blood urea concentration, and strength of the vascular connective tissue. Although platelet dysfunction in liver disease has been experimentally shown to be balanced by increased highly active VonWillebrand factor multimers, the aforementioned remaining factors (especially correctable anemia), have not been considered [1].

Studies on a favourable outcome on bleeding with treatment of anemia in liver disease are worthwhile, especially as similar measures have hugely benefited patients with renal impairment treated with erythropoietin and intravenous iron. Homoncik and colleagues have conducted a randomized, double-blind, placebo-controlled trial of erythropoietin in 22 thrombocytopenic patients with alcoholic liver cirrhosis and have found higher platelet counts and platelet reactivity by flow cytometry in these patients with a more pronounced effect in presence of lower platelet counts [10].

In summary, although “blood component” (plasma products) transfusion may indeed be harmful in liver patients with bleeding tendency, strong consideration should be made for “blood” transfusion, despite its rare adverse effects. It is also worthwhile assessing the response to iron replacement and/or erythropoietin administration in selected patients (bearing in mind thrombotic potential) on the bleeding risk associated with liver disease.

Conflict of interest
The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

References