Liver Transplant Recipients

HCV remains the leading indication for liver transplantation in most transplant centers; interestingly, while the proportion of cases attributable to end-stage liver disease appears to have plateaued, those due to hepatocellular carcinoma (HCC) are rapidly increasing. Unfortunately, the outcome of liver transplantation is impaired in HCV-infected transplant recipients due to recurrent hepatitis C. At least 30% of these individuals may progress to advanced liver disease over a 1 to 7-year period. Many factors are associated with an increased risk of disease progression, but only effective antiviral therapy has proved to have a major impact on the natural history of HCV-associated graft disease. Indeed, viral eradication with antiviral therapy results in histologic, biochemical and clinical improvement resulting in a substantial decrease in the risk of graft-related mortality.

Antiviral therapy with interferon-based regimens is the standard of care. Treatment is usually considered in patients with F2 or F0-1 and significant inflammation based on protocol graft biopsies ± non-invasive monitoring tools (particularly hepatic elastography). Double therapy with peginterferon and ribavirin results in sustained viral response (SVR) rates in the range of 25-40% in patients with HCV genotype 1 and 45-65% in non-1 HCV genotypes. Viral kinetics predict treatment response; if an early viral response evaluated at 12 weeks post-treatment initiation is not achieved, it is highly unlikely that the patient will achieve an SVR with the standard 12-month double therapy. Higher response rates are achieved in those who can tolerate the complete course of aggressive regimens with interferon and particularly ribavirin given at full doses, in those treated before there is progression to cirrhosis, and in those with IL28B CC polymorphism of both the donor and the recipient. Side effects occur very frequently leading to a constrained follow-up, frequent dose reductions or discontinuations, use of granulocyte colony stimulating factor and erythropoietin, hospital admissions and blood transfusions. Most side effects are of hematologic (anemia, neutropenia, thrombocytopenia), or psychiatric nature (depression). In addition, rejection and “de novo autoimmune hepatitis” can be triggered by the use of interferon.

Triple therapies with either telaprevir or boceprevir are now being investigated in this setting, and available data are still preliminary. The main findings from these early studies show that while challenging, in part because treatment is targeting “difficult to treat” patients (prior non-response, advanced fibrosis, high baseline HCV RNA), improved SVRs are expected. Major results to date can be summarized as follows: (i) a high rate of viral response in the first weeks of therapy, about 80% at week 12 (68-100%) and 60% at week 24 (50-65%) with no significant differences between boceprevir and telaprevir-based therapy. Whether this rapid VR will correlate with improved SVR is unknown; (ii) high rate of adverse events, particularly infections (9-18%), haematologic toxicity and renal dysfunction- likely reflecting drug-drug interactions. In particular, anemia occurs almost invariably and results in an extremely frequent use of erythropoietin and ribavirin dose reductions as well as frequent transfusions; and (iii) drug-drug
interactions between calcineurin inhibitors and protease inhibitors a very relevant issue that needs to be acknowledged. Boceprevir and telaprevir are metabolized via the Cytochrome P450 3a system and compete with cyclosporine, tacrolimus, everolimus and sirolimus for metabolism. Emerging data suggest that the area under the curve for these immunosuppressive agents is dramatically increased when given with telaprevir or boceprevir. These interactions are particularly significant between tacrolimus and telaprevir, but can be managed successfully with strict and frequent monitoring of immunosuppressive levels. When starting protease inhibitors, calcineurin inhibitors doses need to be reduced to avoid toxicity while increase of the doses to pre-treatment or even higher doses are required once protease inhibitors are discontinued in order to avoid rejection episodes. In summary, based on these preliminary findings, it is expected that triple therapy will result in a 30%-increase in SVR in liver transplant recipients. However, compared to double therapy, concerns remain regarding toxicity and drug-drug interactions. Future studies should focus on identifying predictors for non-response to avoid unnecessary treatment and associated toxicities.

As in the non-transplant setting, there is great hope for non-interferon based therapies. Apart for the potential for significantly greater efficacy, it is the lack of toxicity and/or potentially fewer drug-drug interactions that make these therapies very attractive. If, in the presence of these new agents, they are still needed for HCV recurrence, it is likely that they will be introduced very early after transplantation before histologic damage occurs. Trials are currently underway to evaluate IFN-free regimes in liver transplant patients (e.g. Expanded Access Program of Sofosbuvir With Ribavirin and With or Without Pegylated Interferon in Aggressive Post-transplant hepatitis C-NCT01779518; Study to Investigate GS-7977 and Ribavirin for 24 Weeks in Subjects With Recurrent Chronic HCV Post liver transplant-NCT01687270).

References


