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OPINIONS

# Transplanting Kidney Allografts from Hepatitis C Infected Donors into Hepatitis C Uninfected Recipients: Re-Thinking the Thinker Trial

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## ABSTRACT

In the not so distant past, organs from hepatitis C infected donors were either discarded or rarely transplanted into HCV viremic recipients - but never allocated to non-infected patients. However, the simplicity, ease and unprecedented success rates of HCV direct acting antiviral regimens has raised the possibility of utilizing such organs in an attempt to expand the donor pool. The thinker trial reports the first of such attempts. However, caution must be exercised prior to the widespread adoption of such strategy.

**Key words.** Hepatitis C. Transplantation. Kidney. Allografts. Direct acting antiviral agents.

The Thinker Trial, a small pilot study by Goldberg, *et al*.[1] is a pioneering work, but its application remains firmly rooted in the experimental realm.

The investigators allocated 10 renal allografts from Hepatitis C (HCV) viremic donors to HCV uninfected recipients and promptly treated them with a 12 week regimen of Elbasvir- Grazoprevir. All ten patients achieved sustained virological response (SVR) at 12 weeks and stable renal allograft function. Despite their encouraging results, a few points need to be highlighted. First, the recipients and donors were highly selected as only ten patients of 285 were transplanted. The extensive exclusion criteria ensured only patients without liver pathology or contraindications to liver transplantation were included in this trial. All donors were HCV genotype 1 infected with no baseline NS5A resistance associated substitutions (RAS) ensuring a high SVR rate with 12 weeks of Elbasvir- Grazoprevir, the direct acting antiviral (DAA) combination rescue therapy. Elbasvir-Grazoprevir is the antiviral of choice in the setting of advanced renal dysfunction, but is only approved for genotype (GT)1 and 4 with an SVR rate of 95% in treatment naïve (TN) individuals.[2] We note that the SVR rate in GT1a can be much lower (58%) with the presence of baseline NS5A RAS, hence the utmost attention to rapid genotyping and baseline resistance testing in this trial. Rapid RAS testing of declared donors, however, is currently not available in a community setting. Even in the most favourable scenario of using a TN GT1 infected allograft, there remains a 5% chance of treatment failure with potentially fatal outcomes. Currently, there are limited treatment options for DAA failures and essentially no options if patients have advanced renal disease. In addition, HCV recurrence in the setting of transplantation and heavy immunosuppression can lead to fibrosing cholestatic hepatitis (FCH), an aggressive and often fatal hepatitis and, if virologically resistant, a contra-indication to liver transplantation. Although DAAs have dramatically improved the cure rates for HCV, their success is not guaranteed. The risk and consequences of treatment failure might be justifiable in a patient requiring liver transplantation, with the certainty of death in the near future but less defensible in patients with ESRD on renal replacement therapy. Until, we have pangenotypic DAAs effective against resistant variants with a good safety profile in renal dysfunction, and access to rapid genotyping and resistance testing of deceased donors, HCV-infected renal allografts should only be utilized in study settings with patients' informed consent.

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