Journal of Autoimmunity xxx (2015) 1–9

Contents lists available at ScienceDirect

Journal of Autoimmunity

journal homepage: www.elsevier.com/locate/jautimm

Review article

An update on liver transplantation: A critical review

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ARTICLE INFO

Article history:
Received 24 August 2015
Accepted 26 August 2015
Available online xxx

Keywords:
Liver transplantation
Machine perfusion
Recurrent disease
Donation after circulatory
Death
De novo cancer

ABSTRACT

Liver transplantation, although now a routine procedure, with defined indications and usually excellent outcomes, still has challenges. Donor shortage remains a key issue. Transplanted organs are not free of risk and may transmit cancer, infection, metabolic or autoimmune disease. Approaches to the donor shortage include use of organs from donors after circulatory death, from living donors and from those previously infected with Hepatitis B and C and even HIV for selected recipients. Normothermic regional and/or machine perfusion, whether static or pulsatile, normo- or hypothermic, are being explored and will be likely to have a major place in improving donation rates and outcomes. The main indications for liver replacement are alcoholic liver disease, HCV, non-alcoholic liver disease and liver cancer. Recent studies have shown that selected patients with severe alcoholic hepatitis may also benefit from liver transplant. The advent of new and highly effective treatments for HCV, whether given before or after transplant will have a major impact on outcomes. The role of transplantation for those with liver cell cancer continues to evolve as other interventions become more effective. Immunosuppression is usually required life-long and adherence remains a challenge, especially in adolescents. Immunosuppression with calcineurin inhibitors (primarily tacrolimus), antimetabolites (azathioprine or mycophenolate) and corticosteroids remains standard. Outcomes after transplantation are good but not normal in quality or quantity. Premature death may be due to increased risk of cardiovascular disease, de novo cancer, recurrent disease or late technical problems.

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Abbreviations: AIH, autoimmune hepatitis; AMR, antibody mediated rejection; BMI, body metabolic index; HBV, hepatitis B Virus; CMV, cytomegalovirus; DBD, donation after brain death; DCD, donation after circulatory death; EBV, epstein Barr virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HEV, hepatitis E virus; HLA, human leucocyte antigen; HTLV, human lymphotrophic virus; LAR, late acute rejection; MELD, model for end-stage liver disease; mTOR, mammalian target of rapamycin; NAT, nucleic acid technology; NAFLD, non-alcoholic liver disease; PBC, primary Biliary cirrhosis or cholangitis; PSC, primary sclerosing cholangitis; UCSF, University of California San Francisco; UKELD, UK model for end-stage liver disease.

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http://dx.doi.org/10.1016/j.jaut.2015.08.021
0896-8411/

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1. Introduction

The pioneering work of Thomas Starzl, Roy Calne, C.S.Welch, J.A.Cannon, Francis Moore and others in the 1950s paved the way for the first successful liver transplant in 1963 by Starzl in Denver, Colorado. Five years later, Sir Roy Calne, supported by Roger Williams, led the first European liver transplant programme in Cambridge, UK. Initially, progress was slow and the mortality of recipients high. It is a great tribute to the early pioneers that they remained persistent in overcoming the many challenges and obstacles; advances in surgical and anaesthetic techniques, greater understanding of the physiological, haematological, biochemical, microbiological and immunological changes in liver disease and transplantation allowed a multidisciplinary approach that led to better outcomes. These changes, coupled with more effective immunosuppressive and anti-microbial agents and improvements in patient and donor selection, mean that now liver replacement is a routine procedure with excellent long term outcomes. This review will focus on some of the current challenges in liver transplantation. This is, therefore, not a comprehensive review, but rather a critical review of the challenges of liver transplantation.

2. Organ shortage

As liver transplantation has become routine and contra-indications removed, the number of potential recipients in increasing. In most jurisdictions, waiting lists, which will underestimate the true need, are increasing; in the UK, up to 18% of adults listed for a first elective transplant will die or become too ill before a graft is available [1]. This fall in the number of donors comes at a time where, in most jurisdictions, the pool of potential donors is falling, in part as a result of better health, fewer road traffic incidents and changes in the management of patients with catastrophic brain injuries, Coincidently, potential donors are becoming older and with a greater BMI [1]. Older donors are more likely to have co-morbidities and a raised BMI, associated with hepatic steatosis, increases the donor risk for the liver. The increasing imbalance between need and availability of deceased donors has resulted in surgeons often working at the boundaries of what is possible within the donor pool. Some of the strategies adopted are outlined in Table 1.

Table 1
Strategies to minimise the impact of the donor shortage.

Using organs from donors at higher risk of disease transmission
Increasing living liver donation
Using organs from donors after circulatory death (DCD)
Using new technologies
Normothermic regional perfusion
Machine perfusion

2.1. Using organs from donors with higher risk

All donated organs are associated with risk but some donors are associated with greater risk. These risks may relate to either the donor or the organ. The surgeon, with the suitably informed and consented patient needs to make a risk analysis: balancing the risks of accepting an organ from a donor with an estimated risk of disease transmission or poor function with the risks of death awaiting the next suitable offer.

2.1.1. Donor risks include the transmission of disease

Donor transmission of cancer: cancers from donors may be donor-transmitted or donor derived. There are several guidelines indicating the risk of cancer transmission from donors with a history of cancer [2]. Of note, a recent review of donor transmitted cancer in the UK showed a risk of less than 0.03%. One common feature was that in no case was it known, before transplantation, that the donor had a cancer [2].

Donor transmission of infections: a wide variety of infections have been transmitted by solid organ transplant. Donor characterisation will exclude or identify a number of infective agents (the screening included Hepatitis B and C, Cytomaglovirus (CMV), Epstein Barr virus (EBV), Human T-lymphotropic virus 1 and 2 (HTLV), Human Immunodeficiency virus (HIV) I and II, Treponema pallidum. Other tests that may be done include assessing malaria, West Nile virus and T cruzi. In the latter cases, the serology may become available only after transplantation. Standard serology may miss some patients with active infection, such as may occur in the window period, where virus is present in blood but before a detectable antibody response. In other cases, rare infection may be missed, such as a recent case of fatal Helicophalabus gingivalis transmission.

The advent of rapid nucleic acid technology (NAT) testing may allow for a more rapid and sensitive evaluation of the donor risk. However, the advent of effective and often curative treatments for Hepatitis B and C and HIV may mitigate the impact of such donor-derived infections. At present, organs from selected donors with

Please cite this article in press as: J. Neuberger, An update on liver transplantation: A critical review, Journal of Autoimmunity (2015), http://dx.doi.org/10.1016/j.jaut.2015.08.021