ABO-incompatible adult living donor liver transplantation in the era of Rituximab - A Systematic Review and Meta-Analysis

INTRODUCTION

Liver transplant (LT) has now become an ideal treatment option for patients with liver cancer and end-stage liver diseases; however, its use is restricted due to the shortage of organ donor pool. In past decades, different attempts and breakthrough have been made to increase the donor pool. One of them is living donor liver transplant (LDLT), this applies both for urgent and elective LT. Moreover, in the shortage of ABO-compatible (ABOc) donor and to increase donor pool, ABO-incompatible (ABOi) LT remains only the option for many with rapid worsening of liver function or who remains on the long waiting list. Taking this into consideration, different innovative B cell desensitization protocols, such as use of total plasma exchange (TPE), double-filtration plasmapheresis, local graft infusion therapy (LGIT), plasmapheresis with rituximab, mycophenolate mofetil (MMF) and intravenous immunoglobulin G (IVIG) has been used to breach the blood group barrier leading to significant advancements in the outcomes of ABO. Thus, ABOi is no more contemplated a contraindication for LT.

ABOi adult LDLT pediatric patients is considered safe and with acceptable results probably because of their immature immune system. However, the safety of ABO adult LDLT (ALDLT) is debatable among transplant community due to different risks associated to it, especially earlier graft loss, acute cellular rejection (ACR), antibody mediated rejection (AMR), vascular, and biliary complications in compared to that of ABOc ALDLT. Effective desensitization protocol for ABO ALDLT is very demand. Consequently, the introduction of rituximab, a anti-CD20 monoclonal antibody to desensitization protocol has brought about a significant reduction in the incidence of AMR and improved the outcomes of ABOi ALDLT. Rituximab acts on the CD20 antigen present on B cell, thus reducing the production of B cell which is mainly responsible for acute rejection and AMR. This study aimed to compare the short and long term outcomes between ABOi ALDLT with rituximab prophylaxis and ABOc ALDLT. HCC recurrence and progression is combative after LT due to immunosuppressive state of patients. Hence, this meta-analysis also aimed to assess hepatocellular carcinoma recurrence and progression is combative after LT due to immunosuppressive state of patients. Hence, this meta-analysis also aimed to assess hepatocellular carcinoma (HCC) recurrence for patients with HCC following ABOi ALDLT with rituximab prophylaxis compared to that of ABOc ALDLT.

METHODS

PubMed, EMBASE, and the Cochrane Library study search were accomplished to recognize studies comparing ABOi and ABOc ALDLT. Meta-analysis were conducted based on the evaluation of heterogeneity using a fixed-effects model and a random-effects model to assess the short-term and long-term outcomes, graft survival, overall survival, and disease free survival for patients with HCC following ABOi ALDLT with rituximab prophylaxis.

RESULTS

Eight studies comprising total 3,858 patients (ABOi= 639 and ABOc= 3,219) were identified. There was no significant difference between ABOi and ABOc groups for 1 year, 3 year and 5 year OS and graft survival, respectively. Moreover, 1 year and 3 year DFS was comparable between both the groups for HCC patients. The incidences of post-operative complications were comparable between both the groups. However, ABOi ALDLT had higher incidence of CMV infection, AMR, and biliary stenosis than that of adult ABOc ALDLT.

CONCLUSION

The significant reduction in the incidence of AMR after introduction of rituximab might be the cause to improve in graft survival of ABOi ALDLT. Currently, there are no definitive answers as why the overall survival of ABOi group didn't differ with ABOc group; however, when we looked for a MELD score between ABOi and ABOc groups, our meta-analysis revealed that MELD of ABOi groups was significantly lower than ABOc group. Additionally, this result is supported by previous studies which stated high MELD score were the risk factor for patient survival after LT. The possible cause of the higher incidence of CMV might be because of the immunocompromised state due to rituximab. Rituximab suppresses different stages of B cell differentiation and leading to rapid decrease in peripheral B cell population within 48-72 hours, and which can last for several months. Furthermore, repeated dosing of rituximab induces prolonged hypogammaglobulinemia which has high risk for serious infectious complications.

Diffuse intrahepatic biliary stricture (DHBS), which is a lessened type of AMR still remains to be the concern in ABOi ALDLT. Moreover, DHBS has been reported to occur following ABOc ALDLT. Although rituximab may thoroughly control AMR over ABO barriers, it doesn't do as such on the ground, that it cannot annihilate plasma cells that are present on the epithelium of the bile ducts, thus leading to DHBS and biliary stricture. This explains why ABOi ALDLT has higher incidence of AMR and biliary stricture.

Our meta-analysis included the largest number of studies comparing ABOi and ABOc ALDLT and those all using rituximab prophylaxis for ABOi ALDLT. ABOi ALDLT showed comparable results with that of ABOc ALDLT. However, biliary complications and antibody-mediated rejection only remains to be concerned in the epoch of rituximab. Thus, suggesting the need for effective and standard desensitization protocol in addition to rituximab in the future.